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HEALTH AND MEDICINE

Childhood adverse life events and skeletal muscle mitochondrial function

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Social stress experienced in childhood is associated with adverse health later in life. Mitochondrial function has been implicated as a mechanism for how stressful life events "get under the skin" to influence physical well-being. Using data from the Study of Muscle, Mobility, and Aging ($n = 879$, 59% women), linear models examined whether adverse childhood events (i.e., physical abuse) were associated with two measures of skeletal muscle mitochondrial energetics in older adults: (i) maximal adenosine triphosphate production (ATP_{max}) and (ii) maximal state 3 respiration (Max OXPHOS). Forty-five percent of the sample reported experiencing one or more adverse childhood events. After adjustment, each additional event was associated with −0.08 SD (95% confidence interval = −0.13, −0.02) lower ATP_{max}. No association was observed with Max OXPHOS. Adverse childhood events are associated with lower ATP production in later life. Findings indicate that mitochondrial function may be a mechanism for understanding how early social stress influences health in later life.

INTRODUCTION

Stressful life events experienced early in the life course have been repeatedly shown to be associated with worse health later in life (*1*–*5*). Yet, the specific mechanism underlying this relationship remains poorly understood. Mitochondrial bioenergetics, hereinafter referred to as "mitochondrial function," is defined by changes in the capacity to generate cellular energy in the form of adenosine triphosphate (ATP) and becomes impaired with age (*6*). Recently, mitochondrial function has been implicated as a possible mechanism for understanding how stressful life events "get under the skin" to influence health and physical well-being (*7*–*12*).

Mitochondria are capable of sensing and integrating social stress on a cellular level (*7*). In response to psychological stress, mitochondria undergo dynamic changes in their structure, leading to alterations in function (*7*). One potential pathway by which early childhood stress may lead to changes in mitochondrial functional capacity may involve an impaired glucocorticoid response (*4*). Persistent oxidative stress that arises from chronic, low-grade inflammation due to a blunted glucocorticoid response is associated with mitochondrial dysfunction (*11*). Specifically, excessive glucocorticoid levels increase calcium buffering capacity, mitochondrial membrane potential, and apoptotic signaling resistance (*11*).

A small number of human studies suggest that stressful social experiences may be associated with changes in mitochondrial function. For example, chronic stress due to caregiving for a family member with a chronic health condition was associated with lower mitochondrial respiratory capacity in blood cells among women (*13*). Childhood maltreatment was found to be associated with changes in mitochondrial cellular respiration in blood cells related to ATP production (*14*). New mothers who had a history of childhood maltreatment had alterations in ATP production, and women with a more severe history of maltreatment had a worse mitochondrial bioenergetic profile in blood cells (*15*).

While these studies provide initial evidence that mitochondrial function may serve as a salient mechanism linking life events in childhood to poor health, two critical gaps remain. First, the majority of studies conducted have used measures of mitochondrial function obtained from whole blood (*9*, *10*, *13*, *14*). Thus, the relationship between adverse childhood events and tissue-specific measures of mitochondrial energetics obtained from skeletal muscle biopsies—the current gold standard—is not known. Work in rodent models has demonstrated that early life stress leads to altered mitochondrial structure and bioenergetics in the peripheral (muscle) and central nervous system (hippocampus) (*16*). These changes were associated with systemic effects on altered metabolic homeostasis and cognitive impairment. However, similar data in human peripheral tissues in response to stress are lacking. Second, prior work in this area has been hampered by small sample sizes (*14*), was exclusively conducted in women (*13*, *15*), or had minimal or no covariate adjustment (*13*–*15*).

In this study, we leverage data from the Study of Muscle, Mobility, and Aging (SOMMA) to examine how stressful life events in childhood may be associated with skeletal muscle mitochondrial function in later life. We extend prior studies by including in vivo and in vitro measures of mitochondrial energetics obtained from 31-phosphorous magnetic resonance spectroscopy (^{31}P MRS) and muscle biopsies in a large, well-characterized sample of older adults. We hypothesized that individuals who have experienced

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greater adverse life events in childhood would have worse mitochondrial bioenergetic profiles in muscle (lower respiratory capacity and lower ATP_{max}) in older age.

RESULTS

Of the 879 participants included in the study, 59% were women, the mean chronologic age was 76.3 years (SD = 5 years), and 86% were self-reported as white. While about half of the sample had completed some college or obtained a college degree (49.9%), only 32% of the respondents' parents completed some college or obtained a college degree. Among the 754 participants who had complete data on childhood adverse life events (cALEs), 53% reported experiencing one or more adverse events in childhood. Among those experiencing three or more events, 55 individuals reported experiencing three events, 29 participants reported four events, 25 participants reported five events, and 8 participants reported experiencing all six events. Individuals who reported experiencing stressful life events in childhood, on average, reported a greater number of depressive symptoms. See Table 1.

Results for the overall sample

After adjusting for age, site, and gender (model 1), each additional cALE was associated with a −0.10 SD lower ATP_{max} [95% confidence interval (CI) = −0.19, −0.01], a statistically significant finding. Adjusting for parental education (model 2) and hypothesized confounder-mediators (model 3) slightly attenuated the association and remained statistically significant, such that each additional adverse event was associated with a −0.08 SD lower ATP_{max} (95% CI = −0.13, −0.02). See Table 2. When examining effect modification by gender, the interaction term was not significant for ATP_{max} ($P = 0.36$) nor for maximal oxidative phosphorylation (Max OXPHOS; $P = 0.78$); however, given previous reports of potential sex differences in mitochondria (*17*, *18*), we analyzed gender-stratified models (Tables 3 and 4) and report results for men and women below.

Results for women

After adjusting for age and site (model 1), each additional adverse life event experienced before the age of 18 was associated with a −0.04 SD lower ATP_{max} (95% = −0.10, 0.02), although the confidence interval included the null value and was not statistically significant. The results, when adding parental education (model 2) and further adjusting for hypothesized confounder-mediators (Model 3), did not change the overall association (Table 3). Although these results were not statistically significant, the effect estimates, while small, were in the anticipated direction and inversely related to cALEs.

Results for men

Among men, each additional adverse life event experienced before the age of 18 was borderline associated with −0.11SD lower ATP_{max} (95% CI = −0.21, −0.00). There was no change in the effect estimate, which remained statistically significant with the inclusion of parental education. The effect estimate was slightly magnified when including participant education, smoking, physical activity, medication use, body mass index (BMI), and depressive symptoms (model 3), such that each additional adverse life event was associated with −0.15 SD lower ATP_{max} (95% CI = −0.25, −0.05) (Table 4), which was statistically significant. Associations were not statistically significant for the Max OXPHOS measure for either women or men and are reported in tables S1 and S2.

DISCUSSION

In this well-characterized sample of older adults with gold-standard measures of mitochondrial bioenergetics, we investigated whether adverse life events experienced before the age of 18 were associated with reduced skeletal muscle mitochondrial function in later life. We found that in the overall sample, each additional adverse life event was associated with modestly lower ATP_{max}, an in vivo measure of maximal capacity for ATP production. In gender-stratified models, significant associations between cALEs and ATP_{max} were observed in men but not in women. In contrast, no association was observed between cALEs and the ex vivo maximum OXPHOS capacity measure in either men or women.

Few studies have explored whether stressful experiences in early life are associated with reduced mitochondrial function, recently recognized as a "hallmark of aging" (*19*) and implicated in the development of a host of aging-related outcomes (*19*–*22*). Several studies have shown how stressful life experiences influence whole-body phenomena such as allostatic load and inflammation (*23*–*25*); however, the biological processes by which these stressful social events experienced early in the life course may lead to impaired skeletal muscle mitochondria bioenergetics have received little attention, especially in the context of human cohort studies with both ex vivo and in vivo measures of bioenergetic function.

The results of our study offer preliminary evidence for the specific role that skeletal muscle mitochondria may play in how adverse events become biologically embedded. While a small number of studies have examined how stressful experiences in early life influence mitochondrial function, to date, much of this previous work has focused on alterations in the content of mitochondrial DNA (mtDNA). For example, adults who have experienced maltreatment in childhood or lost a parent before age 18 had a significantly lower mtDNA copy number compared to those with no adverse events in childhood (*14*). In close to 12,000 Chinese women with and without a history of major depression, childhood sexual abuse was shown to be associated with a greater mtDNA copy number in cells obtained from saliva samples (*26*). In a study of 290 adults, after controlling for perceived stress, resilience, depressive symptoms, and anxiety, the positive relationship between childhood adverse events and the salivary mtDNA copy number remained statistically significant (*10*). In another study of 50 healthy middle-aged adults who were experimentally exposed to a brief psychological stressor (a public speaking simulation), a statistically significant rapid increase in serum circulating cell-free mtDNA was observed shortly after (*27*). Together, given that the mtDNA encodes proteins that influence cellular respiration and other bioenergetic properties, these results provide supporting evidence that core mitochondrial functions may be impaired in the face of social adversity, particularly events experienced early in the life course.

We found that maximal ATP production in muscle was compromised among those who had experienced adverse life events in childhood, even after substantial adjustment. One possible explanation for this finding may lie in what Picard and McEwen defined as a "mitochondrial allostatic load" (MAL), a phenomenon in which mitochondria respond to social stressors that are chronic or severe (*11*, *12*). Specifically, MAL has been described as a multifactorial, dynamic process by which mitochondria exhibit decreased respiratory enzymatic

Table 1. Baseline sample characteristics by childhood adverse life events in the SOMMA study (n = 879). Max OXPHOS, maximal oxidative phosphorylation; HS, high school.

	Number of childhood adverse life events (cALEs)									
	0 (N = 356)		1 (N = 166)		2 (N = 115)		3 + (N = 117)		Total (N = 754)	
	Mean (SD)									
ATP_{max} (mM/s)	0.6	(0.2)	0.5	(0.1)	0.5	(0.2)	0.5	(0.1)	0.5	(0.1)
Max OXPHOS [pmol/(s*mg)]	61.0	(19.7)	58.7	(17.0)	60.4	(18.2)	57.9	(17.5)	59.9	(18.6)
CESD-10 score (0–30 points)	3.5	(3.3)	3.7	(3.3)	4.7	(3.6)	5.5	(4.0)	4.0	(3.5)
Physical activity (cal/week)	3800.2	(3297.2)	3889.6	(3175.7)	3748.0	(2627.1)	3825.3	(3062.4)	3815.8	(3134.8)
Body mass index (kg/m^2)	27.4	(4.6)	27.2	(4.4)	28.8	(4.5)	28.2	(4.6)	27.7	(4.6)
Multimorbidity index (0–12 conditions)	0.8	(0.9)	0.7	(0.9)	0.9	(0.9)	0.8	(0.8)	0.8	(0.9)
Moderate to vigorous physical activity (MVPA; min)	181.9	81.5	189.6	85.5	182.1	87.6	205.0	97.7	187.1	86.1
Age at baseline (years)	76.8	(5.2)	76.3	(5.1)	76.3	(4.7)	74.6	(3.7)	76.3	(5.0)
	N (%)									
Race										
White	311	(87.4)	146	(88.0)	102	(88.7)	91	(77.8)	650	(86.2)
Black	33	(9.3)	18	(10.8)	13	(11.3)	24	(20.5)	88	(11.7)
Asian/Nat Am/Alaska Nat/Multirace	10	(2.8)	1	(0.6)	0	(0.0)	1	(0.9)	12	(1.6)
Unknown	2	(0.6)	1	(0.6)	0	(0.0)	1	(0.9)	4	(0.5)
Gender										
Men	161	(45.2)	64	(38.6)	47	(40.9)	36	(30.8)	308	(40.8)
Women	195	(54.8)	102	(61.4)	68	(59.1)	81	(69.2)	446	(59.2)
Site										
1	172	(48.3)	84	(50.6)	70	(60.9)	51	(43.6)	377	(50.0)
2	184	(51.7)	82	(49.4)	45	(39.1)	66	(56.4)	377	(50.0)
Education										
<HS/HS	50	(14.2)	18	(10.8)	14	(12.2)	15	(12.8)	97	(12.9)
Some college	68	(19.3)	40	(24.1)	30	(26.1)	35	(29.9)	173	(23.0)
College	109	(30.9)	34	(20.5)	27	(23.5)	32	(27.4)	202	(26.9)
Postcollege	126	(35.7)	74	(44.6)	44	(38.3)	35	(29.9)	279	(37.2)
Parental education										
<HS/HS	183	(53.8)	96	(58.9)	67	(62.0)	72	(63.7)	418	(57.7)
Some college	53	(15.6)	22	(13.5)	22	(20.4)	20	(17.7)	117	(16.2)
College	60	(17.6)	27	(16.6)	14	(13.0)	12	(10.6)	113	(15.6)
Postcollege	44	(12.9)	18	(11.0)	5	(4.6)	9	(8.0)	76	(10.5)
Cigarette smoking status										
Never	214	(60.1)	92	(55.4)	53	(46.1)	71	(60.7)	430	(57.0)
Past	132	(37.1)	68	(41.0)	61	(53.0)	44	(37.6)	305	(40.5)

(Continued)

(Continued)

	Number of childhood adverse life events (cALEs)									
	0 (*N* = 356)		1 (*N* = 166)		2 (*N* = 115)		3 + (*N* = 117)		Total (*N* = 754)	
Current	10	(2.8)	6	(3.6)	1	(0.9)	2	(1.7)	19	(2.5)

Table 2. Overall linear regression results examining the relationship between childhood adverse life events and standardized ATP_{Max}.

	Model 1		Model 2		Model 3	
	β	(95% CI)	β	(95% CI)	β	(95% CI)
Intercept	2.04	[0.88, 3.20]	1.99	[0.80, 3.19]	1.16	[−0.26, 2.57]
Childhood adverse life events (cALEs)	−0.10	[−0.19, −0.01]	−0.06	[−0.11, −0.00]	−0.08	[−0.13, −0.02]
Age (years)	−0.02	[−0.04, −0.01]	−0.02	[−0.04, −0.01]	−0.01	[−0.03, 0.01]
Site*	0.25	[0.10, 0.39]	0.28	[0.12, 0.43]	0.29	[0.14, 0.45]
Gender†	−0.37	[−0.56, −0.18]	−0.32	[−0.47, −0.16]	−0.46	[−0.63, −0.29]
Gender × cALEs	0.05	[−0.06, 0.16]				
Parental education‡						
Some college			−0.13	[−0.35, 0.08]	−0.17	[−0.39, 0.05]
College			0.06	[−0.16, 0.28]	0.03	[−0.19, 0.25]
Postcollege			0.04	[−0.21, 0.29]	−0.03	[−0.31, 0.24]
Body mass index (kg/m^2)					0.00	[−0.01, 0.02]
CESD-10 score (0–30 points)					0.02	[0.00, 0.05]
Education‡						
Some college					0.18	[−0.10, 0.46]
College					0.38	[0.10, 0.65]
Postcollege					0.31	[0.04, 0.58]
Moderate to vigorous physical activity (MVPA; min)					0.00	[0.00, 0.00]
Multimorbidity index (0–12)					−0.12	[−0.22, −0.03]
Smoking status§						
Former					−0.11	[−0.27, 0.05]
Current					−0.48	[−0.97, 0.02]

*Reference is the Pittsburgh site. †Reference is women. ‡Reference is <HS/HS. §Reference is never smoker.

activity or mitochondrial membrane potential, which may lead to reduced energy production. This physiologic response is consistent with our finding that ATP_{max}, a measure of maximal energy production, was lower among those who had experienced greater adverse events in childhood. Lower skeletal muscle mitochondrial energetics declines with age and is associated with reduced muscle performance, mobility, and frailty in older adults (*21*, *28*–*31*). Therefore, the association of lower ATP_{max} with cALEs observed in this study suggests that these early life stressors may contribute to reduced health and quality of life in older adults.

We investigated whether the relationship between cALEs and mitochondrial function differed by gender. While we did not find evidence of statistical interaction, we found in gender-stratified models that, among men, each additional adverse life event in childhood was associated with lower ATP_{max}. Although few studies have investigated whether there are gender differences in mitochondrial function in humans, a small body of evidence suggests that sex hormones may shape skeletal muscle metabolism, which may also influence the fiber type composition/size and capillary density (*32*). Therefore, it is possible that the inability to control for these confounding variables may, in part, explain why we observed different results by gender. An alternative reason for this difference may be driven by differential reporting. Prior research indicates that while women are more likely to suffer from post-traumatic stress disorder, men are more likely to report exposure to traumatic events (*33*–*35*).

One unexpected finding was the lack of an observed association between the Max OXPHOS measure and cALEs. There are several potential explanations for this finding. First, while experiencing social stress may be related to a reduced capacity to generate ATP (*36*, *37*), this may occur without impairment to the electron transport system,

Table 3. Linear regression results for women examining the relationship between childhood adverse life events and standardized ATP_{Max}.

	Model 1		Model 2		Model 3	
	β	(95% CI)	β	(95% CI)	β	(95% CI)
Intercept	1.15	[−0.23, 2.54]	1.09	[−0.36, 2.55]	0.81	[−0.88, 2.51]
Childhood adverse life events (cALEs)	−0.04	[−0.10, 0.02]	−0.04	[−0.10, 0.02]	−0.05	[−0.11, 0.01]
Age (years)	−0.02	[−0.03, 0.00]	−0.02	[−0.04, 0.00]	−0.01	[−0.03, 0.01]
Site*	0.12	[−0.05, 0.30]	0.15	[−0.03, 0.33]	0.12	[−0.07, 0.32]
Parental Education†						
Some college			−0.13	[−0.38, 0.12]	−0.19	[−0.45, 0.07]
College			0.13	[−0.14, 0.41]	0.07	[−0.23, 0.37]
Postcollege			0.03	[−0.25, 0.31]	0.04	[−0.28, 0.36]
Body mass index (kg/m^2)					−0.02	[−0.04, 0.00]
CESD-10 score (0–30 points)					0.03	[−0.00, 0.05]
Education†						
Some college					0.13	[−0.19, 0.44]
College					0.29	[−0.07, 0.64]
Postcollege					0.12	[−0.20, 0.45]
Moderate to vigorous physical activity (MVPA; min)					0.00	[0.00, 0.00]
Multimorbidity index (0–12)					−0.06	[−0.19, 0.06]
Smoking status‡						
Former					−0.05	[−0.25, 0.14]
Current					−0.50	[−1.12, 0.12]

*Reference is the Pittsburgh site. †Reference is <HS/HS. ‡Reference is never smoker.

as assessed by respirometry. Specifically, ATP_{max} is an integrated measure that calculates ATP production, while the ex vivo Max OXPHOS measure reports oxygen consumption as a proxy for ATP production. If there is reduced coupling of oxygen consumption to ATP production (lower ratio of phosphate to oxygen), then it could manifest in lower ATP_{max} without influencing the ex vivo Max OXPHOS measure (*38*). Changes in intracellular calcium cycling is another factor beyond respiratory chain capacity that could limit ATP_{max} but would not influence assays of mitochondrial respiration. Thus, the respiration assay used to determine Max OXPHOS uses oxygen and substrate concentrations that are standardized and saturating where there is no calcium cycling, which represents a fundamentally different assay compared to the ATP_{max} assay (*39*). Last, it is possible that measurement error may have been introduced between the two protocols, which could explain the observed differences.

This study had several strengths. First, we used a well-characterized sample of older adults that contained both in vivo and ex vivo measures of mitochondrial function across a large number of participants. To the best of our knowledge, no studies have obtained gold-standard measures of mitochondrial function in a sample of this size. Second, we were able to use life course social exposure data (i.e., parental education, educational attainment, and adverse events experienced in childhood). The merging of gold-standard mitochondrial bioenergetic measures with highly valid and well-regarded measures of the social environment often does not exist within the same participants. Therefore, by leveraging this unique intersection of data, we were able to link adverse life events experienced in childhood, a well-established social exposure (*2*, *40*, *41*), to biologically specific measures of aging. Last, this study represents an important step forward in our understanding of how mitochondrial function—and specifically ATP production measured in tissue with high relevance for cardiometabolic health and physical function—may be implicated in compromised health among older adults later in the life course. Our study results provide initial mechanistic evidence for how early social stress may influence physical functioning and disability in later life (*5*, *42*, *43*), although future studies are needed to corroborate these findings.

Despite these strengths, this study has several limitations. First, we acknowledge the cross-sectional nature of these data, which limits our ability to disentangle the temporal ordering of mediators on the causal pathway. In future studies, we hope to leverage longitudinal data—a recent addition to the SOMMA study—to parse the contribution of intervening factors that link childhood stress to adult health. For example, we note that we do not have retrospective measures on physical activity to assess the potential contribution of physical activity that occurred earlier in the life course. Second, an additional limitation of the current study is the retrospective

Table 4. Linear regression results for men examining the relationship between childhood adverse life events and standardized ATP_{Max}.

	Model 1		Model 2		Model 3	
	β	(95% CI)	β	(95% CI)	β	(95% CI)
Intercept	2.66	[0.67, 4.66]	2.74	[0.70, 4.79]	1.06	[−1.38, 3.50]
Childhood adverse life events (cALEs)	−0.11	[−0.21, −0.00]	−0.11	[−0.22, −0.00]	−0.15	[−0.25, −0.04]
Age (years)	−0.03	[−0.06, −0.01]	−0.03	[−0.06, −0.01]	−0.01	[−0.04, 0.02]
Site*	0.43	[0.17, 0.69]	0.47	[0.20, 0.74]	0.52	[0.26, 0.79]
Parental education†						
Some college			−0.14	[−0.53, 0.24]	−0.10	[−0.48, 0.28]
College			−0.04	[−0.39, 0.31]	−0.03	[−0.36, 0.31]
Postcollege			0.03	[−0.49, 0.55]	−0.21	[−0.72, 0.30]
Body mass index (kg/m^2)					0.03	[−0.00, 0.06]
CESD-10 score (0–30 points)					0.02	[−0.02, 0.06]
Education†						
Some college					0.25	[−0.29, 0.79]
College					0.49	[0.02, 0.97]
Postcollege					0.55	[0.07, 1.04]
Moderate to vigorous physical activity (MVPA; min)					0.00	[0.00, 0.01]
Multimorbidity index (0–12)					−0.16	[−0.31, −0.02]
Smoking status‡						
Former					−0.17	[−0.44, 0.09]
Current					−0.35	[−1.18, 0.47]

*Reference is the Pittsburgh site. †Reference is <HS/HS. ‡Reference is never smoker.

assessment of our primary exposure, cALEs, and the length of time between the cALEs and the assessment of mitochondrial function. Participants' memory may be subject to recall bias if events that occurred earlier in life were more difficult to recall. However, previous research suggests individuals recall the timing of past traumatic events with reasonable accuracy (*42*, *44*). Third, we treated each adverse event with equal weight and did not know the precise timing in which these events occurred (i.e., age 8 versus 18). Thus, we are unable to fully quantify the magnitude or severity of these adverse events across participants. Future work should pinpoint the duration, timing, and severity of the event experienced. Fourth, our sample was predominantly non-Hispanic white and highly educated, limiting the generalizability of our findings. We note that since we used a modified version of the adverse life events questionnaire, generalizing our findings to other studies may pose challenges for external validity. Fifth, we acknowledge the potential for residual confounding, as we do not have data on the period between childhood and older age to control for indirect pathways by which adverse life events may have influenced mitochondrial function. Sixth, it is possible our estimates reflect overadjustment, since several of the covariates included in our models, while potential confounders, could plausibly be hypothesized as mediators as well (i.e., education) (*45*). However, even with the inability to assess the contribution of other variables on the causal pathway and the potential for overadjustment due to controlling for mediators, we nonetheless observed an association between cALEs and ATP_{max}. Our findings serve as a springboard for future studies to investigate (i) how social stress experienced early in the life course influences mitochondrial function in later life and (ii) the mechanistic basis for mitochondrial dysfunction, ideally in larger sample sizes.

There is growing interest in understanding the social determinants of mitochondrial function among older adults. While few studies have investigated the role of early life social stress and mitochondrial function, almost no prior work has evaluated how adverse life events experienced in childhood influence mitochondrial function in a large sample of older adults. Therefore, this study is an important contribution to the literature because it assesses the relationship between cALEs and mitochondrial function in tissue with high relevance for cardiometabolic health and physical function among older adults. Our results suggest that adverse social stress experienced during childhood may be implicated in ATP production, particularly among men. Future work should examine these findings in the context of other relevant biologic pathways—including, but not limited to, inflammation, cell senescence, and mtDNA mutations—and to what extent other mediating factors may also play a role in shaping energy production among older adults across the life course.

MATERIALS AND METHODS

Data and sample population

The SOMMA is a longitudinal, multicenter study of 879 older adults recruited between April 2019 and December 2021 from University of Pittsburgh and Wake Forest University School of Medicine. Eligibility included age of 70 years or older, BMI less than or equal to 40 kg/m^2, dementia-free, no contraindication to a muscle tissue biopsy and magnetic resonance spectroscopy, and the ability to walk 400 m. Participants who appeared as though they might not be able to complete the 400-m walk at the in-person screening visit completed a short-distance walk (4 m) to ensure their walking speed was ≥ 0.6 m/s. Participants who reported active malignancy or advanced chronic disease and/or reported that they were unable to walk ¼ mile or climb a flight of stairs were excluded. Full study details have been described elsewhere (*46*). Among the 754 participants who had data on cALEs, 698 and 633 participants had complete ATP_{max} and Max OXPHOS data, respectively (see fig. S1). All SOMMA participants provided written informed consent, and the study was approved by the WIRB-Copernicus Group (WCG IRB) (20180764).

Measures

Primary exposure: cALEs

As part of the general baseline questionnaire, all study participants were asked to complete a series of questions based on a modified version of the adverse childhood events (ACE-Q), first published by Felitti *et al.* (*47*). Numerous epidemiologic studies have shown a strong link between adverse childhood experiences and adult mental and physical illnesses (*48*–*52*). While prior studies often use the ACE-Q as a template, there is no existing rationale for including the original specific 11 adversities. This is underscored by the fact that subsequent research has shown items can be removed and added, and the cumulative score remains associated with the same physical/mental health outcomes over the life course (*53*, *54*). In our study, six items were administered that assessed the number of adverse life events experienced during childhood ("While you were growing up (under 18) did you experience any of the following?") (*52*). Response items included "Yes," "No," and "Don't know, Prefer not to answer." Examples of items included in this measure were physical abuse ("Did a parent or other adult in the household ever slap, hit, beat, kick, or physically hurt you in any way?) and emotional neglect ("Did you often feel that no one in your family loved you or thought you were important or special?"). A total of six items were summed to create a continuous measure (0 to 6). All items are reported in the Supplementary Materials.

Primary outcome measures

Two measures of skeletal muscle mitochondrial function were used in this study.

1) Max OXPHOS supported by complexes I and II. To obtain the in vitro Max OXPHOS measure, high-resolution respirometry was performed on permeabilized fresh muscle fiber (PMF) bundles. Participants underwent a percutaneous skeletal muscle biopsy in the presence of local anesthesia, and samples were processed as previously described (*28*). Briefly, a Bergstrom cannula with suction was used to collect the specimen from the middle region of the musculus vastus lateralis. The specimen was cleaned and dissected to obtain a small bundle of myofibers that were placed into ice-cold BIOPS media [10 mM Ca-EGTA buffer, 0.1 M free calcium, 20 mM imidazole, 20 mM taurine, 50 mM potassium 2-(*N*-morpholino)-ethanesulfonic acid, 0.5 mM dithiothreitol, 6.56 mM $MgCl_2$, 5.77 mM ATP, and 15 mM phosphocreatine (PCr) (pH 7.1)]. Myofiber bundles weighing approximately 2 to 3 mg were teased apart for chemical permeabilization with saponin. After washing, the PMF bundles were assayed with a standardized substrate uncoupler inhibitor titration protocol in duplicate to assess mitochondrial respiration as described previously (*28*). Briefly, an Oxygraph-2k instrument (Oroboros Inc., Innsbruck, Austria) was used to measure the respiration of the PMF bundles. Specifically, for the measurement of Max OXPHOS supported by complexes I and II (also referred to as Max OXPHOS or state 3 respiration), the following substrates were added: pyruvate (5 mM), malate (2 mM), glutamate (10 mM), succinate (10 mM), and adenosine 5′-diphosphate (4.2 mM). Data were analyzed using DatLab 7.4 software and steady-state O_2 flux was normalized to fiber bundle wet weight.

2) Maximal ATP production (ATP_{max}) was assessed in vivo using ^{31}P MRS as previously described. Briefly, participants lie in a supine position to perform the first bout of repeated isometric knee extension (30 s) against the resistance of an ankle strap. A second bout was adjusted for the length of time of the kicking (18 to 36 s) to achieve adequate PCr breakdown while maintaining pH < 6.8 to avoid acidic conditions inhibiting mitochondrial ATP production (*55*). Data were analyzed in jMRUI v6.0 using a standard value of 24.5 mM for resting PCr. The postexercise recovery PCr levels were used to calculate rates of mitochondrial ATP resynthesis as previously described to obtain ATP_{max} (*56*, *57*).

Covariates

The following covariates were considered as potential confounders or mediators and entered into the model: (i) age, in years; (ii) gender, men/women; (iii) study site, Pittsburgh versus Wake Forest for ATP_{max} models, or technician group for Max OXPHOS models; (iv) educational attainment, a categorical variable that included less than high school/high school, some college, college, and postcollege; (v) parental education (coded the same way as respondent education) where the highest number of years of schooling completed from either parent was used, a proxy measure of childhood socioeconomic position (*58*, *59*); (vi) BMI, defined as weight divided by height in kilograms per square meter; (vii) number of depressive symptoms, a continuous variable as determined as the Center for Epidemiologic Studies Depression Scale (CES-D) (*60*); (viii) smoking status, a categorical variable defined as "Never," "Past," and "Current"; (ix) physical activity, as assessed by actigraphy using the Actigraph GT9X (Actigraph, Pensacola, FL), a two-axis accelerometer with a sample rate of 30 to 100 Hz. We created a continuous variable that represented the mean of time in minutes spent doing moderate to vigorous physical activity (MVPA); and (x) total number of chronic conditions, a summary multimorbidity index based on the Rochester Epidemiology Project, scored 0 to 12 (*61*).

Statistical analysis

Outcome variables were normally distributed and standardized by subtracting the mean value and then dividing by each variable's respective SD to facilitate comparisons. We used linear regression models that examined the association between continuous childhood ALE and both Max OXPHOS and ATP_{max} in separate models in the overall sample. Given initial evidence suggesting there may be gender differences in mitochondrial bioenergetics (*17*, *18*, *28*), we also tested for statistical interaction by gender. We proceeded with the following modeling strategy: Model 1 (base model) adjusted for age, gender (overall model), site, and/or technician; model 2 (confounder model)

adjusted for model 1 and parental education, a hypothesized confounder that is associated with the childhood ALEs and potentially associated with both mitochondrial outcomes measures but precedes the exposure; lastly, model 3 (confounder/mediator model) adjusted for model 2 and variables that could be hypothesized as confounders but are also downstream of the exposure and on the causal pathway. These variables could plausibly serve as potential mediators, which included participant's education, smoking status, depressive symptoms, BMI, physical activity, and number of chronic conditions. We note that this final model may represent overcontrol given the adjustment for potential mediators, and results should therefore be interpreted with caution (*45*). We also fitted these three gender-stratified models. After accounting for missingness across our primary exposure and outcome variables (ATP_{max}, $n = 698$ and OXPHOS, $n = 633$), we performed a complete case analysis. Missingness was between 4 and 5% across all models. Analyses were conducted using SAS 9.4 (Cary, NC).

Supplementary Materials

This PDF file includes:

Fig. S1
Supplementary File
Tables S1 and S2

REFERENCES AND NOTES

1. D. Kuh, Y. Ben-Shlomo, J. Lynch, J. Hallqvist, C. Power, Life course epidemiology. *J. Epidemiol. Community Health.* **57**, 778–783 (2003).
2. R. D. Goodwin, M. B. Stein, Association between childhood trauma and physical disorders among adults in the United States. *Psychol. Med.* **34**, 509–520 (2004).
3. M. D. Hayward, B. K. Gorman, The long arm of childhood: The influence of early-life social conditions on men's mortality. *Demography* **41**, 87–107 (2004).
4. K. K. Ridout, M. Khan, S. J. Ridout, Adverse childhood experiences run deep: Toxic early life stress, telomeres, and mitochondrial DNA copy number, the biological markers of cumulative stress. *Bioessays* **40**, e1800077 (2018).
5. K. A. Duchowny, M. T. Hicken, P. M. Cawthon, M. M. Glymour, P. Clarke, Life course trauma and muscle weakness in older adults by gender and race/ethnicity: Results from the U.S. health and Retirement Study. *SSM Popul. Health* **11**, 100587 (2020).
6. J. Martínez, I. Marmisolle, D. Tarallo, C. Quijano, Mitochondrial bioenergetics and dynamics in secretion processes. *Front. Endocrinol.* **11**, 319 (2020).
7. M. Picard, B. S. McEwen, Psychological stress and mitochondria: A systematic review. *Psychosom. Med.* **80**, 141–153 (2018).
8. M. Picard, M. J. McManus, J. D. Gray, C. Nasca, C. Moffat, P. K. Kopinski, E. L. Seifert, B. S. McEwen, D. C. Wallace, Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory, and transcriptional responses to acute psychological stress. *Proc. Natl. Acad. Sci. U.S.A.* **112**, E6614–E6623 (2015).
9. E. K. Zitkovsky, T. E. Daniels, A. R. Tyrka, Mitochondria and early-life adversity. *Mitochondrion* **57**, 213–221 (2021).
10. A. R. Tyrka, S. H. Parade, L. H. Price, H.-T. Kao, B. Porton, N. S. Philip, E. S. Welch, L. L. Carpenter, Alterations of mitochondrial DNA copy number and telomere length with early adversity and psychopathology. *Biol. Psychiatry* **79**, 78–86 (2016).
11. M. Picard, R.-P. Juster, B. S. McEwen, Mitochondrial allostatic load puts the "gluc" back in glucocorticoids. *Nat. Rev. Endocrinol.* **10**, 303–310 (2014).
12. M. Picard, B. S. McEwen, Psychological stress and mitochondria: A conceptual framework. *Psychosom. Med.* **80**, 126–140 (2018).
13. M. Picard, A. A. Prather, E. Puterman, A. Cuillerier, M. Coccia, K. Aschbacher, Y. Burelle, E. S. Epel, A mitochondrial health index sensitive to mood and caregiving stress. *Biol. Psychiatry* **84**, 9–17 (2018).
14. C. Boeck, A. M. Koenig, K. Schury, M. L. Geiger, A. Karabatsiakis, S. Wilker, C. Waller, H. Gündel, J. M. Fegert, E. Calzia, I.-T. Kolassa, Inflammation in adult women with a history of child maltreatment: The involvement of mitochondrial alterations and oxidative stress. *Mitochondrion* **30**, 197–207 (2016).
15. A. M. Gumpp, C. Boeck, A. Behnke, A. M. Bach, L. Ramo-Fernández, T. Welz, H. Gündel, I.-T. Kolassa, A. Karabatsiakis, Childhood maltreatment is associated with changes in mitochondrial bioenergetics in maternal, but not in neonatal immune cells. *Proc. Natl. Acad. Sci. U.S.A.* **117**, 24778–24784 (2020).
16. S. R. Ruigrok, K. Yim, T. L. Emmerzaal, B. Geenen, N. Stöberl, J. L. den Blaauwen, M. R. Abbink, A. J. Kiliaan, E. M. van Schothorst, T. Kozicz, A. Korosi, Effects of early-life stress on peripheral and central mitochondria in male mice across ages. *Psychoneuroendocrinology* **132**, 105346 (2021).
17. P. M. Miotto, C. McGlory, T. M. Holloway, S. M. Phillips, G. P. Holloway, Sex differences in mitochondrial respiratory function in human skeletal muscle. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **314**, R909–R915 (2018).
18. C. Silaidos, U. Pilatus, R. Grewal, S. Matura, B. Lienerth, J. Pantel, G. P. Eckert, Sex-associated differences in mitochondrial function in human peripheral blood mononuclear cells (PBMCs) and brain. *Biol. Sex Differ.* **9**, 34 (2018).
19. C. López-Otín, M. A. Blasco, L. Partridge, M. Serrano, G. Kroemer, The hallmarks of aging. *Cell* **153**, 1194–1217 (2013).
20. D. C. Chan, Mitochondria: Dynamic organelles in disease, aging, and development. *Cell* **125**, 1241–1252 (2006).
21. A. J. Santanasto, P. M. Coen, N. W. Glynn, K. E. Conley, S. A. Jubrias, F. Amati, E. S. Strotmeyer, R. M. Boudreau, B. H. Goodpaster, A. B. Newman, The relationship between mitochondrial function and walking performance in older adults with a wide range of physical function. *Exp. Gerontol.* **81**, 1–7 (2016).
22. H. A. Parry, M. D. Roberts, A. N. Kavazis, Human skeletal muscle mitochondrial adaptations following resistance exercise training. *Int. J. Sports Med.* **41**, 349–359 (2020).
23. M. S. Clark, M. J. Bond, J. R. Hecker, Environmental stress, psychological stress and allostatic load. *Psychol. Health Med.* **12**, 18–30 (2007).
24. R. P. Juster, B. S. McEwen, S. J. Lupien, Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci. Biobehav. Rev.* **35**, 2–16 (2010).
25. A. G. Cuevas, A. D. Ong, K. Carvalho, T. Ho, S. W. C. Chan, J. D. Allen, R. Chen, J. Rodgers, U. Biba, D. R. Williams, Discrimination and systemic inflammation: A critical review and synthesis. *Brain Behav. Immun.* **89**, 465–479 (2020).
26. N. Cai, S. Chang, Y. Li, Q. Li, J. Hu, J. Liang, L. Song, W. Kretzschmar, X. Gan, J. Nicod, M. Rivera, H. Deng, B. Du, K. Li, W. Sang, J. Gao, S. Gao, B. Ha, H.-Y. Ho, C. Hu, J. Hu, Z. Hu, G. Huang, G. Jiang, T. Jiang, W. Jin, G. Li, K. Li, Y. Li, Y. Li, Y. Li, Y.-T. Lin, L. Liu, T. Liu, Y. Liu, Y. Liu, Y. Lu, L. Lv, H. Meng, P. Qian, H. Sang, J. Shen, J. Shi, J. Sun, M. Tao, G. Wang, G. Wang, J. Wang, L. Wang, X. Wang, X. Wang, H. Yang, L. Yang, Y. Yin, J. Zhang, K. Zhang, N. Sun, W. Zhang, X. Zhang, Z. Zhang, H. Zhong, G. Breen, J. Wang, J. Marchini, Y. Chen, Q. Xu, X. Xu, R. Mott, G.-J. Huang, K. Kendler, J. Flint, Molecular signatures of major depression. *Curr. Biol.* **25**, 1146–1156 (2015).
27. C. Trumpff, A. L. Marsland, C. Basualto-Alarcón, J. L. Martin, J. E. Carroll, G. Sturm, A. E. Vincent, E. V. Mosharov, Z. Gu, B. A. Kaufman, M. Picard, Acute psychological stress increases serum circulating cell-free mitochondrial DNA. *Psychoneuroendocrinology* **106**, 268–276 (2019).
28. T. Mau, L.-Y. Lui, G. Distefano, P. A. Kramer, S. V. Ramos, F. G. S. Toledo, A. J. Santanasto, E. G. Shankland, D. J. Marcinek, M. J. Jurczak, I. Sipula, F. M. Bello, K. A. Duchowny, A. J. A. Molina, L. M. Sparks, B. H. Goodpaster, R. T. Hepple, S. B. Kritchevsky, A. B. Newman, P. M. Cawthon, S. R. Cummings, P. M. Coen, Mitochondrial energetics in skeletal muscle are associated with leg power and cardiorespiratory fitness in the Study of Muscle, Mobility, and Aging. *J. Gerontol. A Biol. Sci. Med. Sci.* **78**, 1367–1375 (2023).
29. K. R. Short, M. L. Bigelow, J. Kahl, R. Singh, J. Coenen-Schimke, S. Raghavakaimal, K. S. Nair, Decline in skeletal muscle mitochondrial function with aging in humans. *Proc. Natl. Acad. Sci. U.S.A.* **102**, 5618–5623 (2005).
30. Q. Tian, B. A. Mitchell, M. Zampino, K. W. Fishbein, R. G. Spencer, L. Ferrucci, Muscle mitochondrial energetics predicts mobility decline in well-functioning older adults: The Baltimore longitudinal study of aging. *Aging Cell* **21**, e13552 (2022).
31. M. Gonzalez-Freire, R. de Cabo, M. Bernier, S. J. Sollott, E. Fabbri, P. Navas, L. Ferrucci, Reconsidering the role of mitochondria in aging. *J. Gerontol. A Biol. Sci. Med. Sci.* **70**, 1334–1342 (2015).
32. A.-M. Lundsgaard, B. Kiens, Gender differences in skeletal muscle substrate metabolism—Molecular mechanisms and insulin sensitivity. *Front. Endocrinol.* **5**, 195 (2014).
33. D. F. Tolin, E. B. Foa, Sex differences in trauma and posttraumatic stress disorder: A quantitative review of 25 years of research. *Psychol. Trauma Theory Res. Pract. Policy* **132**, 959–992 (2008).
34. R. C. Kessler, K. D. Mickelson, D. R. Williams, The prevalence, distribution, and mental health correlates of perceived discrimination in the United States. *J. Health Soc. Behav.* **40**, 208–230 (1999).
35. D. M. Christiansen, M. Hansen, Accounting for sex differences in PTSD: A multi-variable mediation model. *Eur. J. Psychotraumatol.* **6**, 26068 (2015).
36. M. Picard, B. S. McEwen, E. S. Epel, C. Sandi, An energetic view of stress: Focus on mitochondria. *Front. Neuroendocrinol.* **49**, 72–85 (2018).
37. F. Hollis, M. A. van der Kooij, O. Zanoletti, L. Lozano, C. Cantó, C. Sandi, Mitochondrial function in the brain links anxiety with social subordination. *Proc. Natl. Acad. Sci. U.S.A.* **112**, 15486–15491 (2015).
38. G. Layec, J. R. Gifford, J. D. Trinity, C. R. Hart, R. S. Garten, S. Y. Park, Y. L. Fur, E.-K. Jeong, R. S. Richardson, Accuracy and precision of quantitative 31P-MRS measurements of human skeletal muscle mitochondrial function. *Am. J. Physiol. Endocrinol. Metab.* **311**, E358–E366 (2016).

39. D. A. Cardinale, K. D. Gejl, N. Ørtenblad, B. Ekblom, E. Blomstrand, F. J. Larsen, Reliability of maximal mitochondrial oxidative phosphorylation in permeabilized fibers from the vastus lateralis employing high-resolution respirometry. *Physiol. Rep.* **6**, e13611 (2018).
40. D. Baumeister, R. Akhtar, S. Ciufolini, C. M. Pariante, V. Mondelli, Childhood trauma and adulthood inflammation: A meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol. Psychiatry* **21**, 642–649 (2016).
41. K. T. Putnam, W. W. Harris, F. W. Putnam, Synergistic childhood adversities and complex adult psychopathology. *J. Trauma. Stress* **26**, 435–442 (2013).
42. S. Haas, Trajectories of functional health: The "long arm" of childhood health and socioeconomic factors. *Soc. Sci. Med.* **66**, 849–861 (2007).
43. K. Birnie, R. Cooper, R. M. Martin, D. Kuh, A. A. Sayer, B. E. Alvarado, A. Bayer, K. Christensen, S.-I. Cho, C. Cooper, J. Corley, L. Craig, I. J. Deary, P. Demakakos, S. Ebrahim, J. Gallacher, A. J. Gow, D. Gunnell, S. Haas, T. Hemmingsson, H. Inskip, S.-N. Jang, K. Noronha, M. Osler, A. Palloni, F. Rasmussen, B. Santos-Eggimann, J. Spagnoli, J. Starr, A. Steptoe, H. Syddall, P. Tynelius, D. Weir, L. J. Whalley, M. V. Zunzunegui, Y. Ben-Shlomo, R. Hardy, HALCyon study team, Childhood socioeconomic position and objectively measured physical capability levels in adulthood: A systematic review and meta-analysis. *PLOS ONE* **6**, e15564 (2011).
44. E. A. Krall, I. Valadian, J. T. Dwyer, J. Gardner, Recall of childhood illnesses. *J. Clin. Epidemiol.* **41**, 1059–1064 (1988).
45. E. F. Schisterman, S. R. Cole, R. W. Platt, Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology* **20**, 488–495 (2009).
46. S. R. Cummings, A. B. Newman, P. M. Coen, R. T. Hepple, R. Collins, K. K. Ms, M. Danielson, K. Peters, T. Blackwell, E. Johnson, T. Mau, E. G. Shankland, L.-Y. Lui, S. Patel, D. Young, N. W. Glynn, E. S. Strotmeyer, K. A. Esser, D. J. Marcinek, B. H. Goodpaster, S. Kritchevsky, P. M. Cawthon, The Study of Muscle, Mobility and Aging (SOMMA). A unique cohort study about the cellular biology of aging and age-related loss of mobility. *J. Gerontol. A Biol. Sci. Med. Sci.* **78**, 2083–2093 (2023).
47. V. J. Felitti , R. F. Anda, D. Nordenberg, D. F. Williamson, A. M. Spitz, V. Edwards, M. P. Koss, J. S. Marks, Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. *Am. J. Prev. Med.* **14**, 245–258 (1998).
48. V. J. Felitti, R. F. Anda, D. Nordenberg, D. F. Williamson, A. M. Spitz, V. Edwards, M. P. Koss, J. S. Marks, Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *Am. J. Prev. Med.* **14**, 245–258 (1998).
49. K. Petruccelli, J. Davis, T. Berman, Adverse childhood experiences and associated health outcomes: A systematic review and meta-analysis. *Child Abuse Negl.* **97**, 104127 (2019).
50. M. Boullier, M. Blair, Adverse childhood experiences. *Paediatr. Child Health* **28**, 132–137 (2018).
51. M. T. Merrick, K. A. Ports, D. C. Ford, T. O. Afifi, E. T. Gershoff, A. Grogan-Kaylor, Unpacking the impact of adverse childhood experiences on adult mental health. *Child Abuse Negl.* **69**, 10–19 (2017).
52. S. R. Dube, R. F. Anda, V. J. Felitti, D. P. Chapman, D. F. Williamson, W. H. Giles, Childhood abuse, household dysfunction, and the risk of attempted suicide throughout the life span. *JAMA* **286**, 3089–3096 (2001).
53. R. Danielson, G. F. Sanders, An effective measure of childhood adversity that is valid with older adults. *Child Abuse Negl.* **82**, 156–167 (2018).
54. J. P. Mersky, C. E. Janczewski, J. Topitzes, Rethinking the measurement of adversity. *Child Maltreat.* **22**, 58–68 (2017).
55. S. A. Jubrias, G. J. Crowther, E. G. Shankland, R. K. Gronka, K. E. Conley, Acidosis inhibits oxidative phosphorylation in contracting human skeletal muscle in vivo. *J. Physiol.* **553**, 589–599 (2003).
56. M. L. Blei, K. E. Conley, M. J. Kushmerick, Separate measures of ATP utilization and recovery in human skeletal muscle. *J. Physiol.* **465**, 203–222 (1993).
57. C. E. Amara, D. J. Marcinek, E. G. Shankland, K. A. Schenkman, L. S. L. Arakaki, K. E. Conley, Mitochondrial function in vivo: Spectroscopy provides window on cellular energetics. *Methods* **46**, 312–318 (2008).
58. C. E. Currie, R. A. Elton, J. Todd, S. Platt, Indicators of socioeconomic status for adolescents: The WHO health behaviour in school-aged children survey. *Health Educ. Res.* **12**, 385–397 (1997).
59. L. E. Aarø, A. J. Flisher, S. Kaaya, H. Onya, F. S. Namisi, A. Wubs, Parental education as an indicator of socioeconomic status: Improving quality of data by requiring consistency across measurement occasions. *Scand. J. Public Health* **37** (Suppl. 2), 16–27 (2009).
60. P. M. Lewinsohn, J. R. Seeley, R. E. Roberts, N. B. Allen, Center for Epidemiologic Studies Depression Scale (CES-D) as a screening instrument for depression among community-residing older adults. *Psychol. Aging* **12**, 277–287 (1997).
61. M. Vassilaki, J. A. Aakre, R. H. Cha, W. K. Kremers, J. L. S. Sauver, M. M. Mielke, Y. E. Geda, M. M. Machulda, D. S. Knopman, R. C. Petersen, R. O. Roberts, Multimorbidity and risk of mild cognitive impairment. *J. Am. Geriatr. Soc.* **63**, 1783–1790 (2015).

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