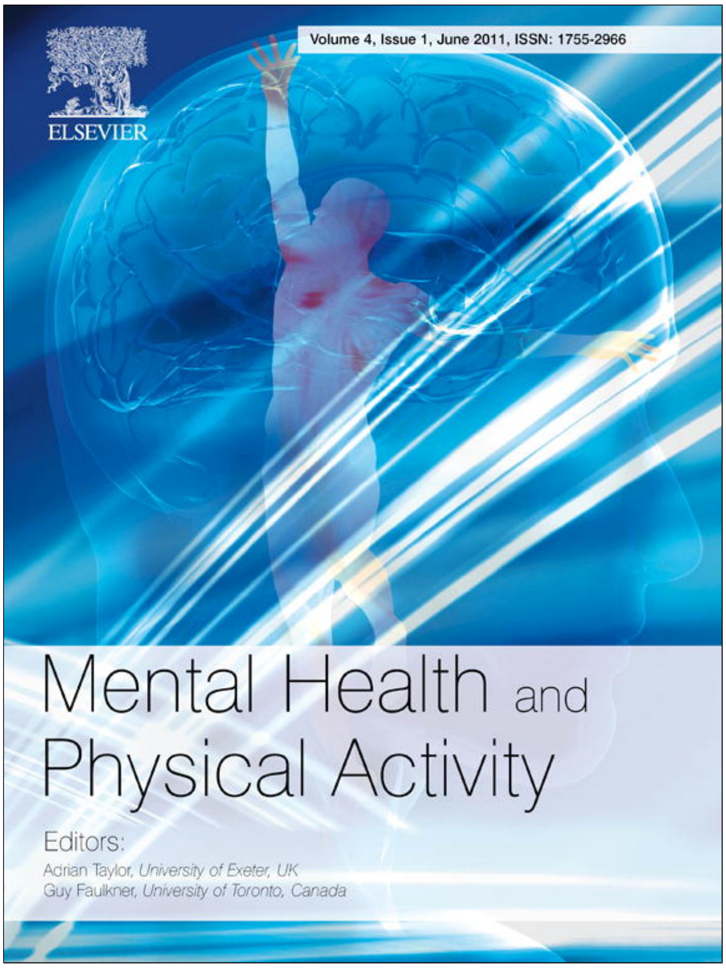
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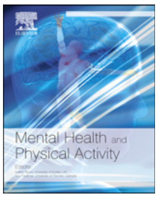

Non-exercise estimated cardiorespiratory fitness: Associations with brain structure, cognition, and memory complaints in older adults

Edward McAuley [a,*], Amanda N. Szabo [a], Emily L. Mailey [a], Kirk I. Erickson [b], Michelle Voss [a], Siobhan M. White [a], Thomas R. Wójcicki [a], Neha Gothe [a], Erin A. Olson [a], Sean P. Mullen [a], Arthur F. Kramer [a]

[a] *University of Illinois, Urbana-Champaign, IL, United States*
[b] *University of Pittsburgh, Pittsburg, PA, United States*

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ABSTRACT

There is increasing evidence that cardiorespiratory fitness (CRF) is associated with brain structure and function, and improvements in CRF through exercise training have been associated with neural and cognitive functioning in older adults. The objectives of this study were to validate the use of a non-exercise estimate of CRF, and to examine its association with cognitive function, brain structure and subjective memory complaints. Low active, older adults ($N = 86$; $Mage = 65.14$) completed a physician-supervised maximal exercise test, a 1-mile timed walk, several measures of cognitive function, and a 3 T structural MRI. Fitness was also calculated from an equation derived by Jurca et al. (2005) based on age, sex, body mass index, resting heart rate, and self-reported physical activity level. Analyses indicated that all three measures of CRF were significantly correlated with one another. In addition, measures of cognitive function, hippocampus volume, and memory complaints were significantly correlated with each measure of fitness. These findings have implications for using a low-risk, low-cost, non-exercise estimate of CRF in determining fitness associations with brain structure and cognitive function in older adults. As such, this measure may have utility for larger population based studies. Further validation is required, as is determination of whether such relationships hold over the course of exercise interventions.

The demographic landscapes of numerous nations are becoming progressively older (United Nations, 2010) with enormous social, economic, and health care implications. Degradations in both cognitive and physical function with aging are well-established (Keysor, 2003; Smith, Betancourt, & Sun, 2005); however, there is encouraging evidence to suggest that following a healthy lifestyle can potentially slow or attenuate these derogatory effects (Desai, Grossberg, & Chibnall, 2010; Hertzog, Kramer, Wilson, & Lindenberger, 2009; Peters, 2009; Rolland, van Kan, & Vellas, 2010). A considerable literature has been generated reporting physical activity and physical fitness to be associated with better cognitive function (Colcombe & Kramer, 2003; Etnier, Nowell, Landers, & Sibley, 2006; Hillman, Erickson, & Kramer, 2008; Lambourne & Tomporowski, 2010), prevention of grey and white matter loss (Colcombe et al., 2006), and enhanced functional brain activity and connectivity (Colcombe, Kramer, McAuley, Erickson, & Scalf, 2004; Voss et al., 2010). However, with respect to the fitness and cognitive function association, there is some debate as to the size of this effect. For example, Smith et al. (2010), in a recent meta-analysis of randomized controlled exercise trials(P. J. Smith et al., 2010), reported a modest but consistent effect for aerobic exercise training on attention and processing speed ($g = .158$), executive function ($g = .123$), and memory ($g = .128$). However, Colcombe and Kramer (2003), in a meta-analysis of exercise training effects on cognitive function in older adults, reported a large effect size ($g = .68$) for exercise training effects on measures of executive function. Regardless of the size of this effect, it appears safe to conclude that the association between fitness and cognitive function is consistent and that the translation of such modest but reliable effects can be projected to have substantial public health benefits for an increasingly older population.

In most adults, engaging in regular aerobic exercise leads to improvements in CRF (Skinner et al., 2001), with vigorously intense exercise conferring greater benefits than moderate-intensity exercise (Kraus et al., 2002; O'Donovan et al., 2005). Some influential findings in the literature, and in particular non-human animal

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[*] Corresponding author. University of Illinois, Department of Kinesiology and Community Health, 906 S. Goodwin Ave., Urbana, IL 61801, United States. Tel.: +217 333 6487; fax: +1 217 333 3124.
E-mail address: emcauley@illinois.edu (E. McAuley).

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studies (Cotman, Berchtold, & Christie, 2007; Gomez-Pinilla, Vaynman, & Ying, 2008; van Praag, 2008; Vaynman & Gomez-Pinilla, 2006), have suggested that increased participation in regular physical activity and improvements in CRF are protective against declines in cognitive function and brain structure (Colcombe et al., 2006, 2004; Erickson et al., 2009; Hassmen & Koivula, 1997; Kramer et al., 1999; Weuve et al., 2004). For example, Kramer et al. (1999) showed improvements in CRF, as a function of participation in a randomized controlled trial, to be associated with an accompanying improvement in cognitive function. Colcombe and Kramer (2003) and Colcombe et al. (2006) extended this work, demonstrating that CRF levels significantly moderated the trajectory of age-related tissue loss. In a follow-up randomized trial, significant increases in brain volume (i.e., in both grey and white matter regions) were found in the older adults who participated in the aerobic fitness training but not for the older adults who participated in a stretching and toning (non-aerobic) comparison group (Colcombe et al., 2006). Specifically, older adults with greater levels of aerobic fitness demonstrated significantly less gray and white matter loss in the frontal (27.3%), temporal (33.7%), and parietal cortices (27.2%). Finally, in a recent cross-sectional study by Erickson et al. (2009), higher levels of CRF were associated with greater hippocampal volume ($\beta = .45$; $p < .001$) and better spatial working memory ($\beta = .29$; $p < .002$) in a sample of older adults.

Unfortunately, the measurement of CRF, particularly in older adults, is challenging in large part due to the constraints of time, resources, and some risks associated with the "gold standard" method of graded exercise testing (GXT). The barriers associated with conducting GXTs may limit the extent to which physical fitness data can be collected. Specifically, the time required to perform such tests can be substantial if the study sample size is large. In addition, the direct expenses (i.e., equipment, trained staff and medical oversight) associated with performing a GXT can be considerable. This is particularly the case when testing older adults who are typically classified as moderate or high risk by the American College of Sports Medicine, necessitating medical supervision (ACSM, 2006). In addition to resource constraints, GXT testing can pose some risk to elderly participants, including injury, heart attack, stroke, or even death (ACSM, 2006). The alternatives to a GXT are typically sub-maximal field tests. Although it is possible to conduct such tests on a relatively large scale, they may still require a significant amount of time and resources and also carry with them some degree of risk. For example, in unfit individuals, a field test such as the Rockport 1-mile walk test (Kline et al., 1987) might require maximal or near maximal effort, thus warranting some level of medical supervision and posing physical risks similar to those described for the GXT. These barriers make it difficult to conduct much needed large-scale interventions or epidemiologic studies to understand the relationship between fitness and cognitive function in older adults.

Recently, Mailey et al. (2010) have validated a relatively simple, low-cost, and low-risk measure of CRF that does not involve exercise testing and has the potential for broad scale use as an estimate of fitness when resources and time do not allow for gold standard exercise testing. This measure, developed initially by Jurca et al. (2005), uses a regression equation to estimate CRF based on sex, age, body mass index (BMI), resting heart rate, and level of physical activity reported on a five category index. Mailey et al. reported the measure to correlate favorably with $V0_{2max}$ assessed by a physician-supervised GXT, a sub-maximal measure of $V0_{2max}$, and cardiovascular risk factors in a sample of older adults. Were such a simple, low-cost measure of fitness to show similar associations with cognitive function and brain structure as have exercise-derived measures of fitness, it may prove valuable to those scientists and clinicians interested in the fitness and cognitive function relationship but who do not have resources to conduct maximal or sub-maximal testing.

The objectives of this study were to validate the use of a non-exercise estimate of CRF, and to examine its association with selective measures of cognitive function, brain structure and subjective memory complaints in a sample of older adults. To do so, we first examined the association of this measure with an estimated measure of CRF based on a 1-mile timed walk test and with the gold standard VO_{2peak} based on a physician-supervised graded maximal exercise test. In turn, we examined the associations of each of these measures of fitness with measures of processing speed, spatial working memory, memory complaints, and brain structure (i.e., hippocampal volume).

1. Method

1.1. Recruitment and participant characteristics

Community dwelling older adults ($N = 86$; $Mage = 65.14$, $SD = 5.09$) from central Illinois, USA were recruited for study participation via local media (e.g., newspaper announcement, radio and television public service announcements, and posting of flyers in the community). Inclusion/exclusion criteria required participants to be between 60 and 80 years of age and not currently physically active. Inclusionary criteria relative to the MRI aspect of the testing required that participants be right handed, have at least 20/40 vision in both eyes (or corrected equivalent), and have no chronic inflammatory diseases or surgically implanted devices. Joint replacements located sufficiently far from the head and thereby unlikely to interfere with the MRI were acceptable. Additional exclusionary criteria included a score below 51 on a modified version of the Mini Mental State Exam (MMSE; Stern, Mayeux, Sano, Hauser, & Bush, 1987), claustrophobia, history of stroke, or depression as classified by the Geriatric Depression Scale (Sheikh & Yesavage, 1986). Prior to testing, all participants were cleared for participation by their personal physician and completed an informed consent form approved by the university institutional review board.

1.2. Measures

1.2.1. Cardiorespiratory fitness: maximal graded exercise test

Participants completed a physician-supervised graded exercise test using a modified Balke protocol (GXT VO_{2peak}; Balke & Ware, 1959; Froelicher, Thompson, Davis, Stewart, & Triebwasser, 1975). Participants walked at a brisk, self-selected pace on a motor-driven treadmill with the incline being increased every 2 min until the participant terminated the test volitionally due to exhaustion or the physician stopped the test due to medical concerns. Peak oxygen consumption (VO_{2peak}; ml/kg/min) was assessed via continuous sampling of expired gases and was indicated as the highest value achieved when meeting two of three standard criteria (i.e., plateau of $VO_{2;}$ reaching age-predicted maximum heart rate; and respiratory exchange ratio (RER) greater than 1.10). Based on these criteria, 69 individuals achieved a $VO_{2\ peak}$. However, 17 individuals reported that they were taking beta blockers at the time of testing. For these individuals a peak was determined if they had a plateau of $VO_{2\ max}$ and RER of greater than 1.10. All individuals volitionally terminated the test.

1.2.2. Cardiorespiratory fitness: estimated by rockport 1-mile walk test

A sub-maximal estimate of CRF was achieved by the Rockport 1-mile walk test (Kline et al., 1987). Participants walked on an enclosed, synthetic track, and were instructed to complete the 1-mile walk as quickly as possible without running. CRF was estimated using one of the following standard, gender-specific Rockport 1-mile walk equations:

a) Estimated VO_{2max} (female) = 154.899 − (.0947*2.2046*weight) − (.3709*age) − (3.9744*walk time) − (.1847*exercise heart rate)
b) Estimated $VO_{2\ max}$ (male) = 116.579 − (.0585*2.2046*weight) − (.3885*age) − (2.7961*walk time) − (.1109*exercise heart rate).

1.2.3. Cardiorespiratory fitness: equation-derived estimate

This estimate of fitness was calculated utilizing the original validation regression equation developed by Jurca et al. (2005), which incorporates a self-reported physical activity (SRPA) index, resting heart rate (RHR), body mass index (BMI), and gender. The SRPA index was determined from a single exercise history question in which participants were asked to identify one of five physical activity categories that reflected their usual pattern of daily physical activity including activities associated with home and family care, transportation, work, exercise and wellness, and leisure or recreation. Level 1 reflected being inactive or doing little activity other than usual daily activities (value = 0); level 2 incorporated regular (≥5 d/wk) participation in physical activities for at least 10 min at a time and requiring low levels of exertion resulting in only slight increases in breathing and heart rate (value = 1); level 3 involved engagement in aerobic exercises such as brisk walking, jogging or running, cycling, swimming, or vigorous sports at a comfortable pace for 20–60 min per week (value = 2); level 4 involved participation in aerobic exercises at a comfortable pace for 1–3 h per week (value = 3); and finally, level 5 reflected participation in aerobic exercises at a comfortable pace for over 3 h per week (value = 4). CRF was expressed in ml/kg/min.

Height and weight were assessed with a Seca electronic scale and stadiometer (Model 763 1321139) with participants wearing light clothing and no shoes. BMI was calculated using the standard formula of weight in kg/height in m^2. RHR was determined using a supine 12-lead electrocardiogram (EKG) tracing, with participants resting quietly for 10 min prior to measurement. CRF was then derived from the following equation:

$$\text{CRF} = \text{Gender}\,(2.77) - \text{Age}\,(.10) - \text{BMI}(.17) - \text{RHR}(.03) + \text{SRPA} + 18.07.$$

1.3. Processing speed

Processing speed was measured by performance on the congruent trials of a modified flanker paradigm (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999). Participants were asked to respond to a central arrow cue embedded in an array of five arrows pointing either left or right. In half of the trials, the flanking arrows were pointed in the same direction as the central arrows reflecting a congruent orientation (e.g., >>>>>). In the other half of the trials, the flanking arrows pointed in the opposite direction to the central arrow reflecting an incongruent orientation (e.g., >><>>). Each participant completed 40 incongruent trials and 40 congruent trials, presented in random order. For the purpose of the present study, we used mean reaction time for the congruent trials as our measure of processing speed.

1.4. Spatial working memory

Spatial working memory was measured by average reaction time (in milliseconds; ms) across three set sizes of a task developed by Greenwood, Lambert, Sunderland, and Parasuraman (2005). Participants were asked to focus on a crosshair for 1 s, at which time one, two, or three black dots (set sizes) appeared randomly on the screen for 500 ms. Following this stimulus the crosshair reappeared for a period of 3 s. Next, a red dot appeared on the screen in either one of the same locations as the target dots (match condition) or at a different location (non-match condition). Participants had 2 s to determine whether the stimulus was a match or non-match, by pressing one of two keys on a standard keyboard. Participants completed 40 trials for each set size (1, 2, or 3 locations), with 20 trials as match trials and 20 trials as non-match trials. Participants were asked to respond as quickly and accurately as possible and allowed several practice trials prior to the test to familiarize themselves with procedures. For the purposes of these analyses, we used the average reaction time across set sizes in our analyses to reflect overall spatial memory reaction time.

1.5. Memory complaints

Participants' memory complaints were assessed using the Frequency of Forgetting questionnaire (Zelinski & Gilewski, 2004). This is a 10-item version of the 33-item Frequency of Forgetting (F of F) scale from the Memory Functioning Questionnaire (MFQ; Gilewski, Zelinski, & Schaie, 1990). Items assess the frequency with which participants have forgotten such things as names, where they have put things, faces, and directions. Items were scored on a seven-point Likert scale with lower scores reflecting a greater frequency of forgetting. Mean ratings were calculated by summing all items and dividing by ten.

1.6. Hippocampus volume

Assessment of hippocampus volume was conducted via images from a 3T Siemens Allegra scanner with an echo time (TE) = 3.87 ms, repetition time (TR) = 1800 ms, field of view (FOV) = 256 mm, an acquisition matrix of 192 × 192 mm, slice thickness of 1.3 mm, and a flip angle of 8°. Segmentation and volumetric analyses were conducted using FMRIB's Integrated Registration and Segmentation Tool (FIRST) in FMRIB's Software Library (FSL; version 4.0). The hippocampus volume comprised the dentate gyrus, the ammonic subfields (CA1–4), the prosubiculum, and the subiculum and did not include the fimbria/fornix behind the posterior commissure. Volume was measured initially in mm^3 and then converted to the more common cm^3 to describe cortical volume. No errors were detected in visible evaluations of each participant's segmentations. Analysis of covariance was used to adjust regional volumes whereby adjusted volume was reflected by raw volume − b × (ICV−mean ICV), where b is the slope of a regression of a region of interest (ROI) volume on intracranial volume (ICV; Head, Rodrigue, Kennedy, & Raz, 2008; Kennedy et al., 2009; Raz et al., 2004, 2005). All subsequent analyses used adjusted volume.

1.7. Procedures

Participants who met all inclusionary criteria and received physician clearance were scheduled to attend four separate testing appointments: the supervised GXT, a neuropsychological testing session, the structural MRI, and the Rockport 1-mile walk test. Testing took place over the course of 2–4 weeks and no two tests were completed on the same day. All participants first completed the neuropsychological battery, then the MRI, followed by the GXT, and finally, the Rockport walking test. Resting heart rate, BMI, and SRPA were collected at the GXT appointment. Each participant also completed a written packet containing a brief demographics questionnaire and the Frequency of Forgetting questionnaire. The cognitive tasks and the MRI scans were completed at a biomedical imaging facility, the GXT completed in an exercise psychology laboratory, and the Rockport test in a university recreation facility. Investigators conducting the cognitive testing and MRI were blinded to participants' CRF values.

1.8. Data analytic strategy

We used Pearson Product Moment correlations to examine the relations among the three measures of CRF and their associations with brain structure, reaction time, and memory complaints. Fisher's r-to-z transformations were then calculated and the z-scores statistically compared (Cohen & Cohen, 1983) to determine whether the correlations between each of the fitness measures and the cognition and brain measures were statistically different. We calculated power based on the relationships between each of the CRF measures and their respective associations with hippocampal volume. Our sample of 86 gave us power in excess of .90 for these analyses.

Finally, we note that almost 20% of our sample was prescribed beta-blockers. Given the importance of heart rate in the assessment of CRF, we also conducted analyses excluding participants on these medications.

2. Results

2.1. Participant characteristics

Table 1 details the descriptive characteristics and health status of the sample. Briefly, participants were predominantly female, white, married, and well-educated. The average modified MMSE score for the sample was 54.85 (SD = 2.42). From a biometric perspective, the sample was low-fit according to the American College of Sports Medicine classifications (2006) and overweight.

2.2. Relationships among three measures of fitness

The equation-derived estimate of CRF was significantly correlated with both the estimated VO $_{2\max}$ ($r = .58$, $p < .001$) and GXT VO $_{2\text{peak}}$ ($r = .68$, $p < .001$). The exercise-derived measures of CRF were significantly related to each other ($r = .66$, $p < .001$). None of these correlations were statistically different from each other (all $ps > .10$). Interestingly, the mean fitness level derived from the GXT ($M = 22.41 \pm 4.47$) and from the Rockport (22.18 ± 6.50) were very similar, whereas fitness derived by equation (25.67 ± 6.50) was higher, suggesting that the equation may over-estimate fitness levels.

Table 1
Descriptive characteristics for study sample.

Variable	Mean (SD)/Frequency (%)
Age	65.3 (5.28)
Sex	
Male	33 (38.4%)
Female	53 (61.6%)
Race	
White	77 (89.5%)
Other	9 (10.5%)
Marital status	
Married	56 (65.1%)
Not married	30 (34.9%)
Education	
4 year college degree or more	36 (41.9%)
Some college or less	50 (58.1%)
Body Mass Index	28.33 (4.09)
Fitness (mL/kg/min)	
CRF measured by GXT	22.41 (4.47)
CRF estimated by Rockport testing	22.18 (7.04)
CRF estimated by equation	25.67 (6.50)
MMSE Score	54.80 (2.41)
Taking heart rate medication	17 (19.8%)
Chronic conditions	
Hypertension	39 (45.3%)
High cholesterol	31 (36.0%)
Diabetes	8 (9.3%)
Osteoporosis	15 (17.4%)
Emotional/mental health disorder	10 (11.6%)

2.3. Relationships among three measures of fitness and cognitive function

2.3.1. Processing speed

CRF based on the Rockport test ($r = -.36$, $p = .001$) and the GXT ($r = -.34$, $p = .05$), and the equation-derived estimate ($r = -.26$, $p = .02$), were significantly associated with mean reaction time to the flanker task congruent task. Fitter participants had faster reaction time. None of these associations were statistically different from each other (all $ps \geq .10$).

2.3.2. Spatial working memory and memory complaints

Fitness was significantly associated with mean spatial working memory reaction time for the GXT-derived measure ($r = -.23$, $p = .05$) and the equation-derived measure ($r = -.29$, $p = .02$) but not the Rockport measure ($r = -.15$, $p = .23$). None of these correlations were statistically significant from each other. Memory complaints, as measured by the Frequency of Forgetting scale, were significantly associated with all measures of fitness: $r = .26$ (Rockport), $r = .31$ (GXT), and $r = .30$ (Equation-derived estimate). Once again, these correlations were not significantly different from each other (all $ps \geq .10$).

2.3.3. Hippocampus volume

All three measures of CRF were significantly associated with hippocampal volume, respectively: GXT ($r = .59$, $p < .001$); Rockport test ($r = .40$, $p < .001$); and the equation-derived estimate ($rs = .41$, $p < .001$). These associations, however, were not significantly different from each other (all $ps \geq .10$).

2.3.4. Analyses excluding beta-blocker participants

All analyses described above were conducted again excluding those individuals being prescribed beta-blockers. Correlations between the equation-derived measure and the exercise measures were virtually unchanged, $r = .54$, (Rockport) and $r = .69$ (GXT). In terms of processing speed, all measures showed slightly stronger correlations with reaction time, $r = .41$ (Rockport), $r = -.39$ (GXT), and $r = -.30$ (Equation-derived estimate). Similarly, there were marginally stronger correlations between spatial working memory reaction time and CRF as measured by Rockport ($r = -.24$), GXT ($r = -.32$), and Equation ($r = .30$). Although none of these were statistically different from the values for the whole sample, the correlation between CRF measured by Rockport and spatial working memory reaction time was now statistically significant ($p = .01$). Finally, the correlations between hippocampus volume and the CRF measures resulted in a marginal increase in the case of GXT ($r = .61$) and small decreases in the correlations with the Rockport ($r = .36$) and equation-derived estimate ($r = .33$). The correlation between hippocampal volume and fitness assessed by the GXT was statistically different from the equation-derived estimate ($p = .03$) and approached significance for the Rockport-derived estimate ($p = .056$).

3. Discussion

We report data which supports the construct validity of an equation-derived estimate of CRF relative to its relationships with brain structure and selected measures of cognition in a sample of older adults. A rapidly growing literature in both animal and human models suggests that physical activity and, in particular, cardiorespiratory or aerobic fitness is implicated in enhanced cognitive function, attenuation of cognitive decline, and the preservation of the aging brain (Kramer, Erickson, & McAuley, 2008). However, much of the methodologically rigorous human research has been conducted on relatively small samples; this shortcoming may be a function of the cost, available resources, and potential risk incurred in large-scale assessments of CRF of older adults using the current gold standard of GXT. One result of this restriction has been to use measures of physical activity to infer fitness associations with outcomes such as brain structure and cognition. This has led to some confusion as to the extent that fitness, exercise, or physical activity confers a protective effect on brain health. Although CRF is a reflection of habitual physical activity, it also has a considerable genetic component, and thus even objective measures of physical activity are questionable as measures of fitness. The development of a reliable and valid non-exercise measure of CRF may represent a solution for conducting larger scale examinations of the fitness and brain health relationship.

To this end, we examined the construct validity of a non-exercise estimate of fitness, developed by Jurca et al. (2005) and validated in older adults by Mailey et al. (2010), in the context of processing speed, spatial working memory, memory complaints, and hippocampal volume in a sample of older adults. In so doing, we compared the equation-derived estimate of fitness against the gold-standard measure of CRF (i.e., physician-supervised GXT) and a submaximal field test estimate (i.e., Rockport 1-mile walk). All three measures were moderately correlated with each other and none of these correlations were significantly different from each other. Consequently, when laboratory assessments and field tests are impractical for reasons of safety, cost, or resources, this non-exercise derived estimate of CRF may be a useful low-cost surrogate. This may especially be the case when large samples are desired or epidemiological studies are planned. If access to biometric data and health records is available, then only the physical activity index would need to be completed in order to calculate estimated CRF. Indeed, it may be possible to estimate values for this index by using existing physical activity data (see Jurca et al., 2005). However, we note that the equation-derived estimate may over-estimate actual CRF when compared to exercise based measures. However, it could also be the case that the exercise-derived measures may be under-estimating fitness in those participants who are prescribed beta blockers. Examining the means of this sub-group supported this position with the equation-derived estimate being significantly higher than both the CRF value from the GXT ($p = .005$) and from Rockport ($p = .001$).

The associations of the equation-derived estimate of fitness with processing speed, spatial working memory, and memory complaints were all significant and were not statistically different from the two exercise-derived measures of fitness. It remains to be determined whether this equation-derived measure of fitness is associated with other aspects of executive function, which have been reported to be influenced by fitness training (Colcombe & Kramer, 2003). Interestingly, we found both the equation- and GXT-derived measures of fitness to be associated with speed of spatial working memory processing. Smith et al. (2010) have reported no effects of aerobic exercise interventions on working memory; however, no analyses of fitness effects were reported. In addition, their analysis combined an array of working memory tasks, whereas our study focused on spatial working memory. Clearly, the exercise–fitness–memory relationship demands further examination, as does the extent to which different measures of fitness differentially relate to working memory.

In the case of memory complaints, less fit individuals reported greater frequency of forgetting, a pattern that held true for all three measures of fitness. Memory problems in older adults have been reported to range from 25 to 60% (De Jager, Blackwell, Budge, & Sahakian, 2005; Jonker, Geerlings, & Schmaud, 2000) and self-appraisals of memory have been associated with subsequent cognitive decline in older adults (Schofield et al., 1997) and with functional brain changes (Small, Larue, Komo, Kaplan, & Mandelkern, 1995). Although Whitbourne, Neupert, & Lachman (2008) have reported that free-living physical activity was associated with fewer memory failures, especially in older adults, the differential relationship between memory complaints and fitness, physical activity, and exercise has largely been ignored. Given that memory complaints are perhaps the most common lay assessment of cognitive health, we suggest that such measures deserve more attention in exercise trials in order to understand the biological, behavioral, and physiological factors that influence these problems.

Recent evidence suggests that fitness is associated with the preservation of hippocampal volume (Erickson et al., 2009). For example, a recent study reported a 12% increase in hippocampal volume in schizophrenic patients and a 16% increase in healthy subjects following a 3-month cycling program. Such a finding has clear implications for how physical activity and, in turn, CRF might have a protective effect on spatial working memory and frequency of memory problems. Results of the present study suggest that all three measures of CRF were correlated significantly with hippocampal volume, with a stronger association evidenced for the gold standard measure. However, the three correlations were not significantly different from each other, providing further construct validity evidence for the equation-derived measure of fitness. It will be important in future studies to establish whether any changes in hippocampal volume brought about by exercise training can be predicted by parallel changes in CRF, as estimated by the Jurca et al. (2005) measure. If this were to be the case, this would be strong evidence to support the use of this simple measure in larger scale studies.

We note that analyses conducted on the sample excluding those participants prescribed heart medications (i.e., beta-blockers) revealed little changes in the findings from the full sample. However, the relationship between CRF and hippocampal volume, although basically unchanged in the smaller sample became statistically different from those correlations involving the two estimated measures of CRF. Thus, we would advise caution in future applications of estimated values of fitness that are based on heart rate and their associations with brain structure. Given that many older adults are prescribed heart medications, the prudent approach would be to analyze data with and without such individuals.

In conclusion, we have presented some initial evidence to suggest that a simple non-exercise estimate of CRF is associated with some elements of brain structure and cognition in a sample of older adults. We acknowledge that our study is not without limitations. First, the sample size is quite small ($N = 86$); although, it might be argued that for a study involving both laboratory and field tests of CRF and structural magnetic resonance imaging it is actually quite a large sample. Second, the data are cross-sectional and a more rigorous test of the construct validity of the equation-derived estimate of fitness will require both longitudinal observational approaches and interventions designed to improve fitness over time. Such approaches will allow for examination of the sensitivity to change of the non-exercise estimate of fitness as well as the relationships between changes in fitness measures and changes in brain structure and function. Finally, our sample was largely female, in relative good health, and of comparatively high social economic status. Future endeavors might be aimed at further evaluating the construct validity of this non-exercise assessment of fitness in randomized controlled trials, in different populations, and in larger samples. An additional potential application of the equation-derived CRF measure is with aging populations with pathological/neurological disorders (e.g., Parkinson's disease), populations who may present additional challenges for conducting standard maximal and sub-maximal CRF assessments. Of particular intrigue is the extent to which this measure might be successfully employed in large-scale population studies in which the basic biometric data are available to combine with the physical activity index in order to determine the fitness and cognitive function relationship in large and diverse samples.

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