Title
When brawn benefits brain: physical activity and Parkinson's disease risk

Journal
Brain, 138(2)

ISSN
0006-8950

Authors
Tanner, Caroline M
Comella, Cynthia L

Publication Date
2015-02-01

DOI
10.1093/brain/awu351

Peer reviewed

BRAIN
A JOURNAL OF NEUROLOGY

SCIENTIFIC COMMENTARIES

When brawn benefits brain: physical activity and Parkinson's disease risk

This scientific commentary refers to 'Physical activity and risk of Parkinson's disease in the Swedish National March Cohort' by Yang *et al.* (doi:10.1093/brain/awu323).

The number of persons with Parkinson's disease is expected to increase dramatically as the world's population ages, with attendant increases in personal and societal burdens (Dorsey *et al.*, 2007). Identifying interventions to lower Parkinson's disease risk is imperative. Moderate to vigorous leisure time exercise was associated with a reduced risk of Parkinson's disease in a meta-analysis of four prospective cohorts in the USA, representing nearly half a million persons (Xu *et al.*, 2010). But leisure time exercise represents <20% of daily physical activity for all but the most dedicated recreational athletes. In this issue of *Brain*, Yang and colleagues provide a more extensive investigation of physical activity and risk of Parkinson's disease by studying total physical activity in a typical 24-h day in a large cohort of Swedish adults (Yang *et al.*, 2014).

The Swedish National March cohort was assembled in 1997 as part of a nationwide cancer awareness effort. More than 40 000 persons, of whom 65% were female, provided detailed information on the duration and intensity of all physical activities, including commuting, household, occupational and leisure activities. Persons newly diagnosed with Parkinson's disease were identified by linking the participants' national registration numbers to inpatient and outpatient diagnostic codes in the Swedish national patient register. Parkinson's disease risk was reduced in males with the highest baseline level of household and commuting activity (>6 h weekly), and in males with the highest overall physical activity, measured in metabolic equivalents. In females, physical activity was not associated with reduced risk of Parkinson's disease. However, in a meta-analysis adding this study to those previously published, higher physical activity was associated with lower risk of Parkinson's disease in both males and females. One limitation of the method used by Yang *et al.* is the reliance on self-report of exercise at a single time point. Also, Parkinson's disease diagnoses were determined by linkage with diagnostic codes, and were not directly verified. The most likely result of these design features would be to attenuate any associations.

Nevertheless, this is the first observation that routine daily physical activity during household chores and commuting can lower the risk of Parkinson's disease. Although exercise has well-established health benefits, including reduced mortality, cardiovascular disease and obesity, <20% of US adults meet recommended standards for leisure time exercise (Johnson *et al.*, 2014). Increasing physical activity during routine daily tasks, such as commuting, may be easier for most people to implement. Simple changes, such as stair climbing instead of taking the elevator, may have important long-term health benefits. The results reported here suggest that reduced risk of Parkinson's disease may be one of them.

The relationship between physical activity and Parkinson's disease risk has biological plausibility. Studies of the effects of exercise in animal models of the disease find that exercise reduces oxidative stress, is associated with release of neuronal growth factors and protects against neuronal injury before or following insults with toxicants [e.g. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-OH dopamine] (Mattson, 2014). Exercise is also associated with lower rates of obesity and type 2 diabetes mellitus. Obesity, high basal metabolic index, and diabetes have been associated with increased risk of Parkinson's disease in some studies. These conditions can cause mitochondrial dysfunction, inflammation and endoplasmic reticulum stress, mechanisms thought to underlie Parkinson's disease (Santiago and Potashkin, 2014). Altered insulin sensitivity may result from physical inactivity, and may increase risk of Parkinson's disease, while anti-diabetic agents that target glucagon-like peptide 1 have been proposed as disease-modifying agents for Parkinson's disease.

Vitamin D levels are low in people with Parkinson's disease (Peterson, 2014), and in one prospective Scandinavian cohort, low vitamin D was associated with increased Parkinson's disease risk. Most of the body's vitamin D is produced as a result of exposure to sunlight. Outdoor

exercise or working outdoors has been associated with lower risk of Parkinson's disease in three populations. In the current study, Yang *et al*. did not determine the location of subjects' physical activity: it is possible that outdoor activity lowered the risk of Parkinson's disease by increasing vitamin D levels.

Physical activity was not associated with a lower risk of Parkinson's disease in females in the study by Yang *et al*. Sexual dimorphism has been observed in a number of other Parkinson's disease risk factors, and the physiological mechanisms behind these gender differences merit further investigation. At present, many of the prospective cohorts are limited to males, and more gender-specific studies are needed. For example, recent studies suggest that females may have physiologically different responses to exercise than males, with a less sustained alteration in metabolic rate and lipid metabolism (Henderson, 2014). These differences in metabolic responses suggest that the duration of physiological benefit from exercise may be reduced in females.

Parkinson's disease has a long prodromal period, and it is possible that reduced physical activity was an early symptom of Parkinson's disease, rather than a cause. In one study, blunted cardiac responses to treadmill exercise were noted years before the development of Parkinson's disease (Palma and Kaufmann, 2014), suggesting that autonomic insufficiency may contribute to lower activity levels in subjects with prodromal disease. Arguing against this explanation is the observation that exercise in young adult life was also associated with the risk of Parkinson's disease in the Swedish National March Cohort, whereas a recent change in exercise was not.

Exercise is also beneficial in preventing conditions associated with prodromal Parkinson's disease, including depression, anxiety and constipation. These observations, combined with the growing body of evidence that physical activity can lower the risk of developing Parkinson's disease, suggest that physical activity may also have a disease modifying effect in people with the disorder (Ahlskog, 2011). In such individuals, physical activity seems to slow progression of motor disability and reduce the risk of developing non-motor features such as depression and cognitive impairment.

The accumulating evidence provides a mandate in support of physical activity, to prevent Parkinson's disease in those unaffected, and to reduce disease burden in subjects with Parkinson's disease. Moderate levels of physical activity, including routine household activities, commuting and outdoor activities, can provide beneficial health effects. The mechanisms responsible are not well understood, and may include increased vitamin D, growth factor release, reduced inflammation, reduced oxidative stress, and a smaller reservoir of fat soluble toxicants. All of these mechanisms may have synergistic effects. Most importantly, moderate physical activity has few adverse effects, and low cost. There seems every reason to respond to the simple command suggested by the name of this national cohort – Forward, March!

Funding

C.M.T. receives grant support from the Michael J. Fox Foundation, the Parkinson's Disease Foundation, the Department of Defense and the National Institutes of Health. C.L.C. receives research support from the NIH R01NS074343, U54NS065701, Dystonia Medical Research Foundation, Allergan Inc. Ipsen Biopharmaceuticals, Inc and Merz Pharmaceutical; and receives research support from the Parkinson's Disease Foundation.

Caroline M. Tanner[1] *and Cynthia L. Comella*[2]

1 *Director, Parkinson's Disease Research Education and Clinical Centre, San Francisco Veteran's Affairs Medical Centre and Department of Neurology, University of California, San Francisco, USA*

2 *Rush Medical Centre, Neurological Sciences, Chicago, Illinois, USA*

Correspondence to: Caroline M. Tanner
E-mail: caroline.tanner@ucsf.edu

doi:10.1093/brain/awu351

References

Ahlskog JE. Does vigorous exercise have a neuroprotective effect in Parkinson disease? Neurology 2011; 77: 288–94.

Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology 2007; 68: 384–6.

Henderson GC. Sexual dimorphism in the effects of exercise on metabolism of lipids to support resting metabolism. Front Endocrinol (Lausanne) 2014; 5: 162.

Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA. CDC National Health Report: leading causes of morbidity and mortality and associated behavioral risk and protective factors-United States, 2005-2013. MMWR Surveill Summ 2014; 63: 3–27.

Mattson MP. Interventions that improve body and brain bioenergetics for Parkinson's disease risk reduction and therapy. J Parkinsons Dis 2014; 4: 1–13.

Palma JA, Kaufmann H. Autonomic disorders predicting Parkinson's disease. Parkinsonism Relat Disord 2014; 20 (Suppl 1): S94–8.

Peterson AL. A review of vitamin D and Parkinson's disease. Maturitas 2014; 78: 40–4.

Santiago JA, Potashkin JA. System-based approaches to decode the molecular links in Parkinson's disease and diabetes. Neurobiol Dis 2014. Advance Access published on April 6, 2014, doi:10.1016/j.ndb.2014.03.019.

Xu Q, Park Y, Huang X, Hollenbeck A, Blair A, Schatzkin A, et al. Physical activities and future risk of Parkinson disease. Neurology 2010; 75: 341–8.

Yang F, Lagerros YT, Bellocco R, Adami HO, Fang F, Pedersen NL, et al. Physical activity and risk of Parkinson's disease in the Swedish National March Cohort. Brain 2015; 138: 269–75.