

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women

"Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women" investigated whether greater cardiovascular fitness in midlife is associated with a decreased risk of dementia in women. The authors found that women with high fitness had a lower adjusted hazard ratio for all-cause dementia and delayed age at onset of dementia compared with women with medium fitness. Commenting on the article, Kivimäki et al. believe that the results are overoptimistic. They explain that because of the small number of dementia cases, the results reported are unlikely to be robust. They support their argument by analyzing an alternative scenario with just 2 additional dementia cases in the high-fitness group, which would decrease the population attributable fraction to less than 60%. Hörder et al. agree that the results may be overoptimistic, but they justify the low number of dementia cases in the highest-fitness group as a consequence of the strong effect of high midlife fitness on dementia risk. They add that high fitness could be regarded as a sum of a number of beneficial factors related to dementia risk (e.g., genetics, exercise, diet, nonsmoking, and blood pressure).

Chafic Karam, MD, and Steven Galetta, MD
Neurology® 2018;91:762. doi:10.1212/WNL.0000000000006349

Reader response: Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women

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Hörder et al.¹ advanced the hypothesis that midlife cardiovascular fitness protects against old-age dementia. However, the limitations of the data were not fully discussed. The estimated benefit of greater fitness in terms of dementia prevention is overoptimistic. Using data from tables 3 and 4 in the article,¹ we calculated a population attributable fraction (PAF) of 78.3%, suggesting that 8 of 10 dementia cases would be avoided if all women had high cardiovascular fitness (table). This is more than 2 times greater than the collective PAF for all known modifiable risk factors in the most recent synopsis,² which is itself an upper-bound estimate.³

Because of the small number of dementia cases, the results reported by Hörder et al. are unlikely to be robust. There were only 2 dementia cases in the high-fitness group; 2 additional cases would lead to a PAF of <60%, whereas 2 fewer cases would lead to the conclusion that women with high fitness do not develop dementia at all. The finding by Hörder et al.¹ is also unlikely to be an "underestimate," as suggested by the accompanying editorial.⁴ Results based on 2 cases could be entirely due to chance.

Author disclosures are available upon request (journal@neurology.org).

Table Population attributable fraction for cardiovascular fitness and dementia in the study by Hörder et al. and an alternative scenario with just 2 additional dementia cases

	Total, N (%)	N (cases)	Dementia proportion	Relative risk	PAF (%)
Cardiovascular fitness					
High	40 (20.9)	2	0.050	1.00	
Medium	92 (48.2)	23	0.250	5.00	41.8
Low	59 (30.9)	19	0.322	6.44	36.5
Total	191 (100)	44			78.3
An alternative scenario with 2 additional dementia cases in the high-fitness group					
High	40 (20.9)	4	0.100	1.00	
Medium	92 (48.2)	23	0.250	2.50	30.0
Low	59 (30.9)	19	0.322	3.22	28.5
Total	191 (100)	46			58.5

Abbreviation: PAF = population attributable fraction.

1. Hörder H, Johansson L, Guo X, et al. Midlife cardiovascular fitness and dementia: a 44-year longitudinal population study in women. *Neurology* 2018;90:e1298–e1305.
2. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017;390:2673–2734.
3. Kivimäki M, Singh-Manoux A. Prevention of dementia by targeting risk factors. *Lancet* 2018;391:1574–1575.
4. Spartano NL, Ngandu T. Fitness and dementia risk: further evidence of the heart-brain connection. *Neurology* 2018;90:675–676.

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Author response: Midlife cardiovascular fitness and dementia: A 44-year longitudinal population study in women

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We are grateful for the comments by Kivimäki et al. on our article.¹ We agree that the effect of dementia prevention in our study is probably overoptimistic. However, the results still suggest that there is a strong effect of midlife cardiovascular fitness on dementia risk in old age. Kivimäki et al. conclude that results based on 2 individuals with dementia are entirely based on chance. However, 44 individuals developed dementia during the 44-year follow-up period. Two of those were in the highest quintile of fitness. The low number of dementia cases in the highest-fitness group is thus the consequence of the strong effect of high midlife fitness on dementia risk. However, as Kivimäki et al. point out, this makes the exact estimation of the benefit of fitness less robust, but it still suggests a strong effect. Kivimäki et al. report that with 2 more cases, the population attributable fraction would decrease from 78% to approximately 60%. We would argue that this is also a strong effect. In addition, high fitness could be regarded as a sum of a number of beneficial factors related to dementia risk (e.g., genetics, exercise, diet, nonsmoking, and blood pressure).

1. Hörder H, Johansson L, Guo X, et al. Midlife cardiovascular fitness and dementia: a 44-year longitudinal population study in women. *Neurology* 2018;90:e1298–e1305.

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Editors' note: Personalizing acute therapies for ischemic stroke: Thrombolysis or thrombectomy?

In the editorial “Personalizing acute therapies for ischemic stroke: Thrombolysis or thrombectomy?,” Drs. Lee and Dziedzic qualified neuroimaging in stroke as the equivalent of precision medicine, personalizing care based on advanced imaging measures. They cited multiple clinical trials demonstrating that endovascular thrombectomy early after acute ischemic stroke (AIS) onset is highly effective for reducing long-term disability. They added that the use of rapid and robust neuroimaging methods that helped select appropriate patients based on clot location or core/penumbra signatures was critical to the success of these trials. The rest of the editorial addressed the work by Bustamante et al., which studied a potential blood biomarker that may help guide therapeutic decision making in the setting of AIS. Commenting on the article, Dr. Munakomi expresses the need to better identify those patients who would benefit from thrombolysis and thrombectomy through stroke awareness via community education and upgrading facilities for teletherapy management. In response, Dr. Lee points to the need for research to enhance diagnostic tests that would help guide the most appropriate and effective treatments in AIS.

Chafic Karam, MD, and Steven Galetta, MD
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Reader response: Personalizing acute therapies for ischemic stroke: Thrombolysis or thrombectomy?

Sunil Munakomi (Biratnagar, Nepal)
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I read with great interest the editorial by Lee and Dziedzic.¹ The advances in imaging armamentarium have enabled us to enroll more patients with ischemic stroke for improved therapy through thrombolysis or thrombectomy. However, only a small subset of these cohort groups is currently benefitting. There is a need to maximize enrollment of such target groups through stroke awareness via community education² and upgrading facilities for teletherapy management.³ These approaches would ensure that ideal candidates receive at least the IV thrombolysis treatment within the vital time window and are then followed up for mechanical thrombectomy.

1. Lee JM, Dziedzic T. Personalizing acute therapies for ischemic stroke thrombolysis or thrombectomy? *Neurology* 2018;90:535–536.
2. Stern EB, Berman M, Thomas JJ, Klassen AC. Community education for stroke awareness: an efficacy study. *Stroke* 1999;30:720–723.
3. Zhai YK, Zhu WJ, Hou HL, Sun DX, Zhao J. Efficacy of telemedicine for thrombolytic therapy in acute ischemic stroke: a meta-analysis. *J Telemed Telecare* 2015;21:123–130.

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Author response: Personalizing acute therapies for ischemic stroke: Thrombolysis or thrombectomy?

Jin-Moo Lee (St. Louis)

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I appreciate Dr. Munakomi's comments, on our editorial,¹ about the importance of public education to increase treatment opportunities for patients with acute ischemic stroke. At the same time, research to enhance diagnostic tests is needed and might help guide the most appropriate and effective treatments. The work by Bustamante et al.² brings us one step closer to a potential blood biomarker that may, one day, help guide therapeutic decision making in the setting of acute ischemic stroke.

1. Lee JM, Dziedzic T. Personalizing acute therapies for ischemic stroke thrombolysis or thrombectomy? *Neurology* 2018;90:535–536.
2. Bustamante A, Ning M, García-Berrocó T, et al. Usefulness of ADAMTS13 to predict response to recanalization therapies in acute ischemic stroke. *Neurology* 2018;90:e995–e1004.

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CORRECTION

Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients

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In the article “Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients” by McCormack et al.,¹ the European Union's Horizon 2020 Research and Innovation Programme was inadvertently omitted from the Study Funding acknowledgment. This project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska-Curie grant agreement no. 751761. The authors regret the omission.

Reference

1. McCormack M, Hongsheng G, Ingason A, et al. Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients. *Neurology* 2018;90:e332–e341.

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Genetic variation in *CFH* predicts phenytoin-induced maculopapular exanthema in European-descent patients

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