

**Comment.** Our main finding was that baseline PPI use was associated with all-cause mortality in 2 cohorts of institutionalized older people. These people may be at high risk of death due to infections, hip fractures, and vascular complications—adverse events that have been associated with PPIs.<sup>1-4</sup> However, our unpublished analyses revealed no association between PPIs and 3-year mortality in 400 home-dwelling cardiovascular patients 75 years or older in the Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study conducted in Helsinki from 2000 through 2003. As with all observational studies there is the possibility of confounding. Proton pump inhibitors may be prescribed for gastroprotection to users of low-dose aspirin, NSAIDs, and SSRIs. However, these drugs were not associated with mortality. Our data highlight the need for urgent research into the risks vs benefits of routinely prescribing PPIs to older people in long-term care.

J. Simon Bell, PhD  
Timo E. Strandberg, MD, PhD  
Mariko Teramura-Gronblad, MD  
Jouko V. Laurila, MD, PhD  
Reijo S. Tilvis, MD, PhD  
Kaisu H. Pitkälä, MD, PhD

**Author Affiliations:** Kuopio Research Centre of Geriatric Care and Clinical Pharmacology and Geriatric Pharmacotherapy Unit, School of Pharmacy, Faculty of Health Sciences, University of Eastern Finland, Kuopio (Dr Bell); Department of Health Sciences/Geriatrics, University of Oulu, and Oulu City Hospital, Oulu, Finland (Dr Strandberg); Unit of General Practice (Drs Teramura-Gronblad and Pitkälä) and Clinics of General Internal Medicine and Geriatrics (Drs Laurila and Tilvis), Helsinki University Central Hospital, Helsinki, Finland; and Home Nursing Services, Helsinki City Health Center, Helsinki (Dr Teramura-Gronblad).

**Correspondence:** Dr Pitkälä, Unit of General Practice, Helsinki University Central Hospital, PO Box 20, 00014 Helsinki, Finland (kaisu.pitkala@helsinki.fi).

**Author Contributions:** Dr Pitkälä had full access to all of the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and is the guarantor. *Study concept and design:* Bell, Strandberg, Teramura-Gronblad, Laurila, Tilvis, and Pitkälä. *Acquisition of data:* Strandberg, Laurila, and Pitkälä. *Analysis and interpretation of data:* Bell and Pitkälä. *Drafting of the manuscript:* Bell, Strandberg, Laurila, and Pitkälä. *Critical revision of the manuscript for important intellectual content:* Teramura-Gronblad, Tilvis, and Pitkälä. *Statistical analysis:* Pitkälä. *Obtained funding:* Laurila and Pitkälä. *Administrative, technical, and material support:* Bell, Strandberg, Tilvis, and Pitkälä. *Study supervision:* Pitkälä.

**Financial Disclosure:** Dr Bell has received grant funding from the Australian Government Department of Health and Ageing and conducted consulting work for Alphapharm Pty Ltd. Dr Strandberg has professional cooperation including consulting/lecturing fees from pharmaceutical and other health care companies (including AstraZeneca, Boehringer Ingelheim, Leiras, MSD Finland, Novartis, Pfizer, and Servier) and has participated

in clinical trials funded by pharmaceutical companies. Dr Laurila has received consulting/lecturing fees from the following pharmaceutical companies: Jansen-Cilag, Lundbeck, Mundipharma, MSD Finland, Pfizer, and Sanofi-Aventis. Dr Tilvis has received lecturing fees from the following pharmaceutical companies: AstraZeneca, Boehringer Ingelheim, Jansen-Cilag, Lundbeck, MSD Finland, Novartis, Orion Pharma, Pfizer, and Sanofi-Aventis. Dr Pitkälä has professional cooperation including receiving lecturing fees from pharmaceutical and other health care companies (including Janssen-Cilag, Leiras, Lundbeck, MSD Finland, Novartis, Pfizer, and Nestle) and has participated in clinical trials funded by pharmaceutical companies.

**Funding/Support:** The data included in the second cohort were collected as part of a study assessing the phenomenology of delirium in acute geriatric wards and nursing homes in Helsinki. This latter study was supported by La Carita Foundation, Uulo Arhio Foundation, and the Helsinki University Central Hospital. The data included in the first cohort were collected as part of a larger study into nutritional care conducted by the City of Helsinki.

**Role of the Sponsors:** The sponsors did not have any role in the study design, analysis or interpretation of data, nor in writing the report or in the decision to submit this research letter for publication. The authors were independent researchers not associated with the funders.

**Additional Contributions:** Heidi Taipale, PhD, provided assistance with data management. We thank the staff of the long-term care wards in Helsinki for their support and participation.

1. Gray SL, LaCroix AZ, Larson J, et al. Proton pump inhibitor use, hip fracture, and change in bone mineral density in postmenopausal women: results from the Women's Health Initiative. *Arch Intern Med.* 2010;170(9):765-771.
2. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. *Arch Intern Med.* 2010;170(9):772-778.
3. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med.* 2007;167(9):950-955.
4. Stockl KM, Le L, Zakharyan A, et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med.* 2010;170(8):704-710.
5. Suominen MH, Sandelin E, Soini H, Pitkälä KH. How well do nurses recognize malnutrition in elderly patients? *Eur J Clin Nutr.* 2009;63(2):292-296.
6. Pitkälä KH, Laurila JV, Strandberg TE, Tilvis RS. Prognostic significance of delirium in frail older people. *Dement Geriatr Cogn Disord.* 2005;19(2-3):158-163.

## Combined Influence of Health Behaviors on Total and Cause-Specific Mortality

A recent article in the *Archives*<sup>1</sup> prospectively examined the individual and collective influence of 4 risk factors (physical activity, diet, smoking, and alcohol consumption) on total and cause-specific mortality. In the Health and Lifestyle Survey (HALS), adjusted hazard ratios and 95% confidence intervals (CIs) for total mortality associated with 1, 2, 3, and 4 poor health behaviors compared with none were 1.85 (95% CI, 1.28-2.68), 2.23 (95% CI, 1.55-3.20), 2.76 (95% CI, 1.91-3.99), and 3.49 (95% CI, 2.31-5.26), respectively (*P* value for trend, <.001). Only a handful of population-based studies<sup>2-4</sup> have examined the com-

**Table. Collective Health Behaviors in Relation to 15-Year Mortality Risk in 2897 Blue Mountains Eye Study Participants (Age >50 y) at Baseline (1992-1994)**

No. of Poor Health Behaviors	Patients, No. (%)	Deaths, No. (%)	Mortality, Adjusted HR (95% CI) <sup>a</sup>		
			All-Cause (n=808)	CVD (n=429)	Cancer (n=268)
0	636 (27.9)	205 (32.2)	1 [Reference]	1 [Reference]	1 [Reference]
1	1020 (44.7)	361 (35.4)	1.07 (0.90-1.28)	1.01 (0.80-1.29)	1.01 (0.75-1.37)
2	473 (20.7)	168 (35.5)	1.23 (1.00-1.52)	1.15 (0.86-1.53)	1.19 (0.83-1.69)
3	130 (5.7)	61 (46.9)	2.25 (1.68-3.01)	1.82 (1.17-2.83)	2.08 (1.28-3.37)
4	24 (1.1)	13 (54.2)	4.58 (2.57-8.15)	4.45 (1.91-10.40)	4.34 (1.71-11.01)
<i>P</i> value for linear trend			<.001	.005	.002

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio.

<sup>a</sup>Adjusted for age, sex, occupational prestige, body mass index, blood pressure, prior diagnosis of heart disease, angina, myocardial infarction, hypertension, stroke, cancer, diabetes mellitus, and asthma.

combined effect of these behaviors on mortality. We investigated whether the collective influence of similar poor health behaviors as detailed by Kvaavik et al<sup>1</sup> influenced the risk of total and cause-specific mortality in a cohort of older Australian adults.

**Methods.** The Blue Mountains Eye Study (BMES-1) is a population-based cohort study of sensory loss and other health outcomes, with methods previously reported.<sup>5</sup> During 1992 through 1994, 3654 participants 49 years or older were examined (82.4% participation). At 5-year follow-up examinations (BMES-2), 2335 surviving participants (75.1% of participants; 543 had died) were examined. Of the 2335 survivors in BMES-2, 1952 (75.6% of survivors; 1103 persons died) were re-examined at 10-year follow-up examinations (BMES-3).

To identify and confirm persons who died after the baseline examination, participants were cross-matched with Australian National Death Index data<sup>6</sup> for deaths until the end of December 2007 (15-year follow-up). Total and cause-specific mortality were assessed using the *International Classification of Diseases, Ninth Revision* definitions, as used in the HALS.<sup>1</sup> We used similar methods to define health behaviors and to generate an index ranging from 0 to 4, as detailed by Kvaavik et al.<sup>1</sup> However, our physical activity measures included not only exercise during leisure time as in the HALS but also other activities such as walking or work-related exercise. We defined poor physical activity as less than 3 times per week. Because we did not have detailed information on arterial disease, bronchitis, emphysema, tuberculosis, and other respiratory tract diseases, these comorbidities were not adjusted for in the multivariable model.

**Results.** Of the 3654 participants at baseline, 2897 had information on all 4 risk factors: 14.2% were current smokers, 20.3% reported poor drinking behavior, 18.4% consumed less than 4 servings per day of fruits and/or vegetables, and 55.1% reported participating in physical activity for less than 3 times per week. The adjusted hazard ratio for 4 poor health behaviors compared with none for all-cause mortality was 4.58 (95% CI, 2.57-8.15), and the corresponding effect estimates for cardiovascular disease and cancer mortality were 4.45 (95% CI, 1.91-10.40) and 4.34 (95% CI, 1.71-11.01), respectively (**Table**). Compared with

participants without any poor health behaviors, the mortality risk for each outcome increased progressively with greater number of poor health behaviors (*P* value for trend, <.01). The difference in  $\beta$  coefficients between a health score of 0 vs 4 was 1.45, equivalent to approximately 14 years in chronological age for mortality risk.

**Comment.** The collective effect of poor health behaviors on mortality was substantial in our older cohort, with BMES participants who engaged in all 4 poor health behaviors having a 4-fold greater risk of total, cardiovascular disease, and cancer mortality compared with those exhibiting none of these behaviors. This is relatively similar to the 3-fold increase in mortality risk observed in the younger HALS cohort.<sup>1</sup> Furthermore, in HALS, the mortality risk for those with 0 compared with 4 poor health behaviors was equivalent to being 12 years younger in chronological age—similar to the 14-year difference observed in our study and in the European Prospective Investigation of Cancer–Norfolk study.<sup>2</sup> Hence, data from both the BMES and HALS provide further supportive evidence that even modest differences in lifestyle and diet could make a significant difference to health at both the individual and population level.

Bamini Gopinath, PhD  
Victoria M. Flood, PhD  
George Burlutsky, MAppStat  
Paul Mitchell, MD, PhD

**Author Affiliations:** Centre for Vision Research, Department of Ophthalmology, Westmead Millennium Institute (Drs Gopinath and Mitchell and Mr Burlutsky), Menzies Centre for Health Policy, University of Sydney (Dr Gopinath), and School of Health Sciences, University of Wollongong (Dr Flood), University of Sydney, New South Wales, Australia.

**Correspondence:** Dr Mitchell, Centre for Vision Research, University of Sydney, Westmead Hospital, Hawkesbury Road, Westmead, NSW 2145, Australia (paul\_mitchell@wmi.usyd.edu.au).

**Author Contributions:** Study concept and design: Gopinath and Mitchell. Acquisition of data: Flood and Mitchell. Analysis and interpretation of data: Gopinath, Flood, Burlutsky, and Mitchell. Drafting of the manuscript: Gopi-

nath. *Critical revision of the manuscript for important intellectual content:* Gopinath, Flood, Burlutsky, and Mitchell. *Statistical analysis:* Burlutsky. *Obtained funding:* Mitchell. *Administrative, technical, and material support:* Flood. *Study supervision:* Mitchell. **Financial Disclosure:** None reported.

1. Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR. Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. *Arch Intern Med.* 2010;170(8):711-718.
2. Khaw KT, Wareham N, Bingham S, Welch A, Luben R, Day N. Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. *PLoS Med.* 2008;5(1):e12.
3. Knoops KT, de Groot LC, Kromhout D, et al. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HAILE project. *JAMA.* 2004;292(12):1433-1439.
4. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB. Combined impact of lifestyle factors on mortality: prospective cohort study in US women. *BMJ.* 2008;337:a1440.
5. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia: the Blue Mountains Eye Study. *Ophthalmology.* 1995;102(10):1450-1460.
6. Wang JJ, Liew G, Wong TY, et al. Retinal vascular calibre and the risk of coronary heart disease-related death. *Heart.* 2006;92(11):1583-1587.

## COMMENTS AND OPINIONS

### Chocolate Intake, Depression, and Clinical Progression in HIV-HCV Coinfected Patients: Still More Questions Than Answers

Rose and colleagues<sup>1</sup> reported intriguing results showing that elevated chocolate intake was found in individuals with probable major depression (as defined by a Center for Epidemiologic Studies Depression Scale [CES-D] score of  $\geq 22$ ), whatever the sex of the individual.

Although one review has already concluded that there is no evidence that chocolate has a significant impact on depression,<sup>2</sup> the interrelationship among elevated chocolate intake, depression, and clinical progression of human immunodeficiency virus (HIV) or hepatitis C virus (HCV) may be particularly fascinating in the HIV-HCV-positive population for several reasons. These individuals have a history of drug injection and/or alcohol abuse, which may both be detrimental to HIV treatment adherence and response.

While further research could better elucidate the protective effect of cocoa on alcohol-induced liver injury,<sup>3</sup> depressive symptoms remain highly prevalent in this population and have been found to be associated with HIV clinical progression, independently of adherence.<sup>4</sup>

We used the first 3 years of follow-up data from the French HEPAVIH ANRS (Agence National pour la recherche sur le Sida et les hépatites [French National Agency for AIDS and Hepatitis Research]) CO-13 cohort to investigate the relationship between chocolate intake and depression more thoroughly at all annual visits for patients not receiving HCV treatment or antidepressants (N=574). At each of these visits, chocolate use was

assessed through self-reports of the frequency of intake in the previous 6 months, while depression was measured using the CES-D.

At enrollment the study group comprised mainly men (70%), with a median (interquartile range [IQR]) CD4 cell count of 450/ $\mu$ L (305-646/ $\mu$ L); 62% were HIV-infected through drug use, 47% and 29% presented with possible or major depression, respectively (CES-D score,  $\geq 16$  or  $\geq 22$ , respectively); and 10% reported no chocolate intake, while 13% reported daily intake.

When studying the relationship between chocolate intake and probable major depression, individuals who did not consume chocolate were more likely to present probable major depression (odds ratio, 1.8, [95% confidence interval, 1.2-2.7];  $P = .006$ ). This relationship remained valid ( $P = .001$ ) after using French sex-specific CES-D cut-off scores for probable depression ( $>17$  for men and  $>23$  for women).

It is difficult to say whether this inconsistency with the results of the study by Rose et al<sup>1</sup> is due to the multiple comorbidities affecting HIV-HCV-positive individuals, which may impair their neuropsychological function,<sup>5</sup> or whether it is due to the differences in cocoa percentages in French chocolate. At any rate, in Europe, dark chocolate must contain at least 35% chocolate liquor, while in the United States, a minimum of 15% chocolate liquor is required for the product to be designated as dark chocolate.

The fact that the complex relationship between chocolate intake and depression remains unclear will probably not be a major barrier to enjoying chocolate and its potential benefits.

M. Patrizia Carrieri, PhD  
Julien Cohen, MS  
Maria Winnock, PhD  
Dominique Salmon, MD

**Author Affiliations:** INSERM, U912 (SE4S), Université Aix Marseille, IRD, UMR-S912, and ORS PACA, Observatoire Régional de la Santé Provence Alpes Côte d'Azur, Marseille, France (Dr Carrieri and Mr Cohen); INSERM U897-ISPED, Bordeaux, France (Dr Winnock); and Institut Cochin, Université Paris-Descartes, INSERM U567-CNRS (UMR 8104), Paris, France (Dr Salmon).

**Correspondence:** Dr Carrieri, INSERM U912 (SE4S), Université Aix Marseille, IRD, UMR-S912, ORS PACA, 23 Rue S Torrents, Marseille 13006, France (Pmcarrieri@aol.com).

1. Rose N, Koperski S, Golomb BA. Mood food: chocolate and depressive symptoms in a cross-sectional analysis. *Arch Intern Med.* 2010;170(8):699-703.
2. Parker G, Parker I, Brotchie H. Mood state effects of chocolate. *J Affect Disord.* 2006;92(2-3):149-159.
3. McKim SE, Konno A, Gabele E, et al. Cocoa extract protects against early alcohol-induced liver injury in the rat. *Arch Biochem Biophys.* 2002;406(1):40-46.
4. Bouhnik AD, Préau M, Vincent E, et al; MANIF 2000 Study Group. Depression and clinical progression in HIV-infected drug users treated with highly active antiretroviral therapy. *Antivir Ther.* 2005;10(1):53-61.
5. Clifford DB, Evans SR, Yang Y, Gulick RM. The neuropsychological and neurological impact of hepatitis C virus co-infection in HIV-infected subjects. *AIDS.* 2005;19(suppl 3):S64-S71.