therefore, conclusions could not be drawn regarding the safety of the zoster vaccine in the population we described. The case reported by Dr Young highlights the need for caution or possibly withholding zoster vaccination in highly immunosuppressed patients.

T. Craig Cheetham, PharmD, MS
Southern California Permanente Medical Group
Pasadena, CA

1. Cheetham TC, Marcy SM, Tseng HF, et al. Risk of herpes zoster and disseminated varicella zoster in patients taking immunosuppressant drugs at the time of zoster vaccination. *Mayo Clin Proc*. 2015;90(7):865-873.

http://dx.doi.org/10.1016/j.mayocp.2016.04.014

The Different Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Mortality

To the Editor: The article by Bangalore et al[1] published in the January 2016 issue of *Mayo Clinic Proceedings* deals with the important topic of cardiovascular protection. In this regard, several recent studies have compared the 2 classes of cardioprotective drugs, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). As highlighted by Bangalore et al, these studies have often reported mortality reduction with ACE inhibitors vs placebo or comparators, while ARBs were not associated with significant effect.

In this new meta-analysis[1] of trials that included patients with diseases ranging from hypertension to myocardial infarction or diabetes, but excluding heart failure, the authors confirmed that ACE inhibitors significantly lower mortality whereas placebo and ARBs do not. Moreover, the authors provided a hypothesis for this difference: ACE inhibitors were discovered and studied in large randomized trials earlier than ARBs. According to them, in view of the improvement in standard of care over the years, concomitant use of lifesaving drugs such as antiplatelet agents or statins was more likely in patients enrolled in ARB trials. This difference could have contributed to the lower impact of ARBs on mortality. To support this hypothesis, the authors suggested that the rate of mortality and morbidity were higher in the placebo groups of ACE inhibitor trials compared with the placebo groups of ARB trials.

This proposal, however, is not supported by the rate of events in Tables 1 and 2 in their article. Indeed, ACE inhibitor trials lasted on average 3.2 years and ARB trials 3 years. The trials included in their analysis provided a follow-up of roughly 99,836 patient-years for ACE inhibitors and 99,423 patient-years for ARBs. The rate of death was therefore 0.0243 events per patient-year in the placebo arms of ACE inhibitor trials and 0.0299 events per patient-year in the placebo arms of ARB trials. As a consequence, and in contrast with the authors' hypothesis, the rate of death tended to be higher in the placebo groups of ARB trials compared with ACE inhibitor trials.

In addition, my colleagues and I observed in a meta-analysis of studies in patients with hypertension performed since 2000 that ACE inhibitor use was again significantly associated with reduced all-cause mortality by 10% vs the comparator, whereas the ARBs had no such association.[2,3] Savarese et al[4] similarly reported a reduction in mortality with ACE inhibitors vs placebo (−9%; P=.008), while no significant effect was detected with ARBs. Contrary to the assumption of Bangalore et al, in trials considered in the meta-analysis by Savarese et al, the coprescription of statins or aspirin was higher in the ACE inhibitor trials compared with ARB trials (51% vs 33% for statins and 85% vs 27% for aspirin). Therefore, the different effects of ACE inhibitors and ARBs cannot be due to different coadministration of lifesaving agents.

In conclusion, it is possible to compare ACE inhibitors and ARBs in a balanced way, at least when restricting the analysis to contemporary trials in patients with hypertension, and in this context, ACE inhibitors are the only class to show a significant reduction of mortality.

Jean-Jacques Mourad, MD, PhD
Avicenne University Hospital
Bobigny, France

Potential Competing Interests: The author reports receiving honorarium for consultancy from several pharma developing ACE inhibitors or ARBs, including Daiichi Sankyo, Menarini, BMS, Servier, Bayer.

1. Bangalore S, Fakheri R, Toklu B, Ogedegbe G, Weintraub H, Messerli FH. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? insights from 254, 301 patients from randomized trials. *Mayo Clin Proc*. 2016;91(1):51-60.
2. van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. *Eur Heart J*. 2012;33(16):2088-2097.
3. Brugts JJ, van Vark L, Akkerhuis M, et al. Impact of renin-angiotensin system inhibitors on mortality and major cardiovascular endpoints in hypertension: a number-needed-to-treat analysis. *Int J Cardiol*. 2015;181:425-429.
4. Savarese G, Costanzo P, Cleland JG, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol*. 2013;61(2):131-142.

http://dx.doi.org/10.1016/j.mayocp.2016.04.021

In Reply—The Different Effects of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Mortality

Dr Mourad contends that the angiotensin-converting enzyme inhibitors (ACEis) are the only drug class to produce a major reduction in

TABLE. Comparison of the Effect of ACEis on Mortality in 3 Contemporary Meta-analyses

ACEi trial	Year published	Comparison	Bangalore et al[3] (sensitivity analysis for placebo trials published after 2000)	Saravese et al[2]	van Vark et al[1]
BENEDICT[4]	2004	Placebo	X		
CAMELOT[5]	2004	Placebo	X	X	
DEMAND[6]	2011	Placebo	X		
DIABHYCAR[7]	2004	Placebo	X	X	
DREAM[8,9]	2006	Placebo	X	X	
EUROPA[10]	2003	Placebo	X	X	
Hou et al[11]	2006	Placebo	X		
IMAGINE[12]	2008	Placebo	X	X	
PEACE[13]	2004	Placebo	X	X	
PHARAO[14]	2008	Placebo	X		
PREAMI[15]	2006	Placebo	X		
PREVEND IT[16]	2004	Placebo	X		
PROGRESS[17]	2001	Placebo	X	X	
QUIET[18]	2001	Placebo	X	X	
QUINS[19]	2007	Placebo	X		
QUO VADIS[20]	2001	Placebo	X		
RASS[21]	2009	Placebo	X		
Wang et al[22]	2012	Placebo	X		
ADVANCE[23]	2007	Placebo			X
HYVET[24]	2008	Placebo			X
AIPRI[25]	1996	Placebo		X	
Lewis et al[26]	1993	Placebo		X	
PART-2[27]	2000	Placebo		X	
SCAT[28]	2000	Placebo		X	
ALLHAT[29,30]	2002	Chlorthalidone or amlodipine			X
ANBP2[31,32]	2003	HCTZ			X
ASCOT-BPLA[33]	2005	Atenolol +/− bendroflumethiazide			X
HYVET-pilot[34]	2003	Thiazides			X
JMIC-B[35]	2004	Nifedipine			X
HOPE[36-38]	2000	Atenolol		X	
ACEi vs controls (as reported in the publication)			0.89 (0.76-1.05)	0.91 (0.85-0.98)	0.90 (0.84-0.97)

ACEis = angiotensin-converting enzyme inhibitors; ADVANCE = Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation; AIPRI = Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ANBP2 = Second Australian National Blood Pressure Study; ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm; BENEDICT = Bergamo Nephrologic Diabetes Complications Trial; CAMELOT = Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis; DEMAND = Delapril and Manidipine for Nephroprotection in Diabetes; DIABHYCAR = Non-Insulin-Dependent Diabetes, Hypertension, Microalbuminuria or Proteinuria, Cardiovascular Events, and Ramipril; DREAM = Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; EUROPA = European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease; HCTZ = hydrochlorothiazide; HOPE = Heart Outcomes Prevention Evaluation; HYVET = Hypertension in the Very Elderly Trial; IMAGINE = Ischemia Management With Accupril Post-Bypass Graft via Inhibition of the Converting Enzyme; JMIC-B = Japan Multicenter Investigation for Cardiovascular Diseases-B; PART-2 = Prevention of Atherosclerosis with Ramipril Trial; PEACE = Prevention of Events With Angiotensin Converting Enzyme Inhibition; PHARAO = Prevention of Hypertension in Patients With High-Normal Blood Pressure With the Angiotensin-Converting-Enzyme-Inhibitor Ramipril; PREAMI = Perindopril and Remodeling in Elderly with Acute Myocardial Infarction; PREVEND IT = Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROGRESS = Perindopril Protection Against Recurrent Stroke Study; QUIET = Quinapril Ischemic Event Trial; QUINS = Quinapril in Scleroderma; QUO VADIS = Quinapril on Vascular ACE and Determinants of Ischemia; RASS = Renin-Angiotensin System Study; SCAT = Simvastatin/Enalapril Coronary Atherosclerosis Trial.

mortality even in contemporary practice and that angiotensin receptor blockers (ARBs) have no such effect. To support this position, he cites the data from his own meta-analysis[1] and that of Savarese et al.[2] This position is flawed for the simple but inescapable fact that no head-to-head trial of ACEis vs ARBs in patients without heart failure has documented a mortality advantage of ACEis. Head-to-head comparison trials are the only way to accurately test whether there is a mortality benefit of ACEis over ARBs. In fact, our analysis of 7 head-to-head randomized trials of ARBs vs ACEis with 22,422 participants revealed that no such mortality benefit exists (relative risk, 0.98; 95% CI, 0.90-1.07).[3] Our analysis was very well powered (92%) to identify at least a 15% reduction in mortality with ACEis. The results of head-to-head comparison trials trump any indirect inference of ACEis and ARBs and confirms our conclusion that the effect of ACEis and ARBs are largely similar.[3]

Why are the results of the 3 meta-analyses for the end point of mortality different? The Table compares the 3 meta-analyses and the trials included in each. Savarese et al[2] and van Vark et al[1] combined both placebo-controlled trials and active-control trials (which is problematic), whereas we analyzed placebo-controlled trials separately from the active-control trials. Moreover, the number of placebo-controlled trials included in our analysis is far greater than that in either of the other 2 meta-analyses. The results of van Vark et al[1] are driven by trials such as ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm) and HYVET (Hypertension in the Very Elderly Trial), which are not ACEi trials. In both of these trials, ACEi was used as an add-on, if needed, and only a proportion of randomized patients received ACEis. Moreover, they included the ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and Diamicron MR Controlled Evaluation) trial, which was a trial of a fixed-dose combination of perindopril and indapamide compared with placebo. It is therefore not acceptable to consider these trials as purely ACEi trials. Thus, a combination of the inclusion of trials that are inappropriate or conducted before 2000 and the exclusion of a large number of placebo-controlled trials in the 2 meta-analyses drives the difference in results among the 3 analyses. Finally, Supplemental Table 5 in our article provides the placebo death rate for the ACEi and ARB trials (2.65%/y vs 2.05%/y), and it is clear that the placebo death rate is higher in the ACEi trials. The discordance between this rate and the rate calculated by Mourad is due to a computational error. Dr Mourad used the average follow-up duration across all trials (placebo/active control) and not just the placebo-controlled trial follow-up period to calculate placebo event rates. In addition, he did not consider the weight of each of the trials. Each trial provides a certain weight for the overall analysis based on event rate and sample size.

Similarly, the results of van Vark et al[1] and Savarese et al[2] fail to explain why the mortality benefit of ACEis (if there truly is one) is not seen in head-to-head comparison trials of ACEis vs ARBs. Ours is the only meta-analysis that ties together the results of placebo-controlled trials, active-control trials, and head-to-head comparison trials, all of which reveal that the outcomes between ACEis and ARBs in patients without heart failure are largely similar.

Sripal Bangalore, MD, MHA
Robert Fakheri, MD
New York University School of Medicine
New York, NY

Bora Toklu, MD
Mount Sinai Beth Israel Medical Center
New York, NY

Franz H. Messerli, MD
University Hospital
Bern, Switzerland
Icahn School of Medicine at Mount Sinai
New York, NY

Potential Competing Interests: Dr Bangalore has received honoraria from Abbott, Boehringer Ingelheim, Daiichi Sankyo, Merck, Gilead, and Pfizer. Dr Messerli has received consulting fees from Daiichi Sankyo, Pfizer, Takeda, Abbott, AbbVie, Servier, and Ipca Laboratories.

1. van Vark LC, Bertrand M, Akkerhuis KM, et al. Angiotensin-converting enzyme inhibitors reduce mortality in hypertension: a meta-analysis of randomized clinical trials of renin-angiotensin-aldosterone system inhibitors involving 158,998 patients. *Eur Heart J*. 2012;33(16):2088-2097.
2. Savarese G, Costanzo P, Cleland JG, et al. A meta-analysis reporting effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients without heart failure. *J Am Coll Cardiol*. 2013;61(2):131-142.
3. Bangalore S, Fakheri R, Toklu B, Ogedegbe G, Weintraub H, Messerli FH. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients without heart failure? insights from 254,301 patients from randomized trials. *Mayo Clin Proc*. 2016;91(1):51-60.
4. Ruggenenti P, Fassi A, Ilieva AP, et al; Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Engl J Med*. 2004;351(19):1941-1951.
5. Nissen SE, Tuzcu EM, Libby P, et al; CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study; a randomized controlled trial. *JAMA*. 2004;292(18):2217-2225.
6. Ruggenenti P, Lauria G, Iliev IP, et al; DEMAND Study Investigators. Effects of manidipine and delapril in hypertensive patients with type 2 diabetes mellitus: the Delapril and Manidipine for Nephroprotection in Diabetes (DEMAND) randomized clinical trial. *Hypertension*. 2011;58(5):776-783.
7. Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Ménard J; DIABHYCAR Study Investigators. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study) [published correction appears in *BMJ*. 2004;328(7441):686]. *BMJ*. 2004;328(7438):495.
8. DREAM Trial Investigators. Effect of ramipril on the incidence of diabetes. *N Engl J Med*. 2006;355(15):1551-1562.
9. DREAM Trial Investigators. Effects of ramipril and rosiglitazone on cardiovascular and renal outcomes in people with impaired glucose tolerance or impaired fasting glucose: results of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial. *Diabetes Care*. 2008;31(5):1007-1014.

10. European Trial on Reduction of Cardiac Events With Perindopril in Stable Coronary Artery Disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362(9386):782-788.
11. Hou FF, Zhang X, Zhang GH, et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. *N Engl J Med*. 2006;354(2):131-140.
12. Rouleau JL, Warnica WJ, Baillot R, et al; IMAGINE (Ischemia Management With Accupril Post-Bypass Graft via Inhibition of the Converting Enzyme) Investigators. Effects of angiotensin-converting enzyme inhibition in low-risk patients early after coronary artery bypass surgery. *Circulation*. 2008;117(1):24-31.
13. PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351(20):2058-2068.
14. Lüders S, Schrader J, Berger J, et al; PHARAO Study Group. The PHARAO study: prevention of hypertension with the angiotensin-converting enzyme inhibitor ramipril in patients with high-normal blood pressure: a prospective, randomized, controlled prevention trial of the German Hypertension League. *J Hypertens*. 2008;26(7):1487-1496.
15. PREAMI Investigators. Effects of angiotensin-converting enzyme inhibition with perindopril on left ventricular remodeling and clinical outcome: results of the randomized Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) Study. *Arch Intern Med*. 2006;166(6):659-666.
16. Asselbergs FW, Diercks GF, Hillege HL, et al; Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation*. 2004;110(18):2809-2816.
17. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack [published corrections appear in *Lancet*. 2001;358(9292):1556 and *Lancet*. 2002;359(9323):2120]. *Lancet*. 2001;358(9287):1033-1041.
18. Pitt B, O'Neill B, Feldman R, et al; QUIET Study Group. The QUinapril Ischemic Event Trial (QUIET): evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol*. 2001;87(9):1058-1063.
19. Gliddon AE, Doré CJ, Black CM, et al. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. *Arthritis Rheum*. 2007;56(11):3837-3846.
20. Oosterga M, Voors AA, Pinto YM, et al. Effects of quinapril on clinical outcome after coronary artery bypass grafting (the QUO VADIS Study). *Am J Cardiol*. 2001;87(5):542-546.
21. Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. *N Engl J Med*. 2009;361(1):40-51.
22. Wang N, Zheng Z, Jin HY, Xu X. Treatment effects of captopril on non-proliferative diabetic retinopathy. *Chin Med J (Engl)*. 2012;125(2):287-292.
23. Patel A; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370(9590):829-840.
24. Beckett NS, Peters R, Fletcher AE, et al; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358(18):1887-1898.
25. Maschio G, Alberti D, Janin G, et al; Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study Group. Effect of the angiotensin-converting-enzyme inhibitor benazepril on the progression of chronic renal insufficiency. *N Engl J Med*. 1996;334(15):939-945.
26. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD; Collaborative Study Group. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med*. 1993;329(20):1456-1462.
27. MacMahon S, Sharpe N, Gamble G, et al; PART-2 Collaborative Research Group. Randomized, placebo-controlled trial of the angiotensin-converting enzyme inhibitor, ramipril, in patients with coronary or other occlusive arterial disease. *J Am Coll Cardiol*. 2000;36(2):438-443.
28. Teo KK, Burton JR, Buller CE, et al. Long-term effects of cholesterol lowering and angiotensin-converting enzyme inhibition on coronary atherosclerosis: the Simvastatin/Enalapril Coronary Atherosclerosis Trial (SCAT). *Circulation*. 2000;102(15):1748-1754.
29. Barzilay JI, Davis BR, Cutler JA, et al; ALLHAT Collaborative Research Group. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med*. 2006;166(20):2191-2201.
30. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [published corrections appear in *JAMA*. 2003;289(2):178 and *JAMA*. 2004;291(18):2196]. *JAMA*. 2002;288(23):2981-2997.
31. Chowdhury EK, Owen A, Ademi Z, et al; Second Australian National Blood Pressure Study Management Committee. Short- and long-term survival in treated elderly hypertensive patients with or without diabetes: findings from the Second Australian National Blood Pressure study. *Am J Hypertens*. 2014;27(2):199-206.
32. Wing LM, Reid CM, Ryan P, et al; Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting—enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348(7):583-592.
33. Dahlöf B, Sever PS, Poulter NR, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366(9489):895-906.
34. Bulpitt CJ, Beckett NS, Cooke J, et al; Hypertension in the Very Elderly Trial Working Group. Results of the pilot study for the Hypertension in the Very Elderly Trial. *J Hypertens*. 2003;21(12):2409-2417.
35. Yui Y, Sumiyoshi T, Kodama K, et al; JMIC-B Study Group. Comparison of nifedipine retard with angiotensin converting enzyme inhibitors in Japanese hypertensive patients with coronary artery disease: the Japan Multicenter Investigation for Cardiovascular Diseases-B (JMIC-B) randomized trial. *Hypertens Res*. 2004;27(3):181-191.
36. Bosch J, Yusuf S, Pogue J, et al; HOPE Investigators. Use of ramipril in preventing stroke: double blind randomised trial. *BMJ*. 2002;324(7339):699-702.
37. Dagenais GR, Yusuf S, Bourassa MG, et al; HOPE Investigators. Effects of ramipril on coronary events in high-risk persons: results of the Heart Outcomes Prevention Evaluation Study. *Circulation*. 2001;104(5):522-526.
38. Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients [published correction appears in *N Engl J Med*. 2000;342(10):748]. *N Engl J Med*. 2000;342(3):145-153.

http://dx.doi.org/10.1016/j.mayocp.2016.04.020

Decisive Bearing of Organizational Dynamics on the Application and Success of Hospital-Based Cardiac Rehabilitation

To the Editor: Analyses and reviews regarding cardiac rehabilitation (CR) are frequently featured in top-tier journals.[1,2] Cardiac rehabilitation is a comprehensive secondary prevention program involving exercise training as well as medical evaluation, cardiac risk factor modification, education, and counseling.[1] It been established as one of 9 performance measures for patients with ischemic heart disease by the American College of Cardiology Foundation and other preeminent medical organizations,[3] and it has growing relevance amid present-day surges of obesity, sedentariness,