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In Reply We recently reported that high body mass index (BMI) and low aerobic fitness in a large cohort of 18-year-old Swedish men were associated with increased risk of hypertension in adulthood. Hypertension was ascertained using all inpatient diagnoses nationwide throughout the study period (1969-2012) and outpatient diagnoses from all specialty clinics between 2001 and 2012. We indicated that hypertension was therefore underreported because we lacked outpatient data before 2001 or from primary care clinics. Dr Brunström raises the question of whether our findings may be attributable to the known associations between high BMI or low aerobic fitness and coronary heart disease or stroke that are likely to receive inpatient or specialty clinic treatment and are also associated with hypertension.

We performed sensitivity analyses to explore this possibility further. We found that only a small minority of men who were diagnosed with hypertension (n = 93 035) had a concurrent or earlier diagnosis of ischemic heart disease (n = 13 523 [14.5%]) or stroke (n = 5368 [5.8%]). When we repeated our analyses after excluding these individuals, the findings were largely unchanged. High BMI and low aerobic capacity remained associated with an increased risk of hypertension, independent of family history and socioeconomic factors (BMI, overweight or obese vs normal: incidence rate ratio [IRR], 2.62; 95% CI, 2.57-2.67; $P < .001$; aerobic capacity, lowest vs highest tertile: IRR, 1.43; 95% CI 1.39-1.46; $P < .001$). Alternatively, adjusting for ischemic heart disease and stroke as time-dependent variables yielded very similar results. Other findings also were unchanged: high BMI and low aerobic capacity had a negative additive and multiplicative interaction ($P < .001$), and low aerobic capacity remained a significant risk factor among those with normal BMI (lowest vs highest tertile: IRR, 1.52; 95% CI 1.48-1.57; $P < .001$). These supplemental findings suggest that the associations we reported were not spuriously caused by ascertainment bias or confounding by ischemic heart disease or stroke.

Our findings are also consistent with other epidemiologic and biologic evidence linking obesity or low aerobic fitness with a higher risk of developing hypertension. A number of smaller epidemiologic studies have reported similar associations between high BMI[1,2] or low aerobic fitness[3,4] and risk of hypertension. These studies ascertained hypertension in various ways, including direct blood pressure measurements,[3] chart review,[4] or self-report.[1,2] Experimental studies have shown that the underlying mechanisms are multifactorial and involve increased catecholamine secretion and activity, insulin resistance, and other neuroendocrine and metabolic effects on sympathetic activation and endothelial and vascular dysfunction.[5,6] Because associations between obesity or low aerobic fitness and hypertension are well-established, the main purpose of our study was to explore their interactive effects.

We found that high BMI and low aerobic fitness in late adolescence were associated with higher long-term risk of hypertension and had a negative interaction. These findings are congruent with a large body of epidemiologic and biologic evidence and did not appear to be caused by ascertainment bias or confounding. The preponderance of evidence suggests that measures to prevent hypertension should begin early in life and include not only weight control, but aerobic fitness even in persons of normal weight.

Casey Crump, MD, PhD
Jan Sundquist, MD, PhD
Kristina Sundquist, MD, PhD

Author Affiliations: Department of Family Medicine and Community Health, Icahn School of Medicine at Mount Sinai, New York, New York (Crump); Center for Primary Health Care Research, Lund University, Malmö, Sweden (J. Sundquist, K. Sundquist).

Corresponding Author: Casey Crump, MD, PhD, Department of Family Medicine and Community Health, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1077, New York, NY 10029 (casey.crump@mssm.edu).

Conflict of Interest Disclosures: None reported.

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Questioning Nicotine Replacement Therapy Without Behavioral Support

To the Editor We enjoyed reading the article by Cunningham et al[1] in a recent issue of *JAMA Internal Medicine* that demonstrated an effect of mailing smokers nicotine replacement therapy (NRT) without behavioral support on 6-month abstinence from smoking.[1] One important reason for performing this trial, as noted by the authors, was that "population survey data comparing those who used NRT (obtained over-the-counter) during a quit attempt and those who did not use NRT has found no association between use of NRT and an increase in success rates."[1(p185)] This statement refers to a cross-sectional study and a prospective cohort study we recently performed in England.[2,3] However, Cunningham et al did not register the crucial distinction we made in these 2 studies between NRT bought over-the-counter and used without behavioral support and NRT received on prescription (NRT Rx) and used with brief advice from the prescribing physician. Compared with unaided quitting, NRT bought over-the-counter was indeed not effective whereas NRT Rx was (cross-sectional study,[2] odds ratio [OR], 1.62; 95% CI, 1.33-1.94; and prospective cohort study,[3] OR, 1.55; 95% CI, 1.11-2.16).

In the trial by Cunningham et al, smokers interested in quitting within 1 week received nicotine patches along with "a cover letter instructing them on the use of the patches and advising them to talk to their physician or pharmacist if they had any further questions."[1(p186)] While this represented excellent advice and produced a very solid effect, it was somewhat different from the way smokers normally use NRT when bought over-the-counter as assessed in our studies. Another possible factor is that smokers were proactively approached and had to give verbal consent to a longitudinal study in which they had to submit saliva samples to verify their abstinence from smoking at 3 time points. They also received a financial incentive of $20 at each time point to return the saliva sample.

The current study makes an important contribution to the literature in demonstrating an effect of NRT in the most naturalistic trial to date. We also acknowledge that conducting these types of pragmatic trials is an incredibly difficult (and admirable) topic for research. However, we suggest that the findings of the current study do not necessarily contradict the previous failure to find an effect of NRT just bought from a shop, though they do point to a wide-reach, low-intensity way of providing NRT that is effective.

Daniel Kotz, PhD
Jamie Brown, PhD
Robert West, PhD

Author Affiliations: Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany (Kotz); Department of Family Medicine, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre, Maastricht, the Netherlands (Kotz); Cancer Research UK Health Behaviour Research Centre, University College London, London, England (Kotz, Brown, West).

Corresponding Author: Daniel Kotz, PhD, Institute of General Practice, Medical Faculty of the Heinrich-Heine-University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany (Daniel.Kotz@med.uni-duesseldorf.de; website, http://www.daniel-kotz.de).

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2. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. *Addiction*. 2014;109(3):491-499.

3. Kotz D, Brown J, West R. Prospective cohort study of the effectiveness of smoking cessation treatments used in the "real world". *Mayo Clin Proc*. 2014;89(10):1360-1367.

In Reply The article by Cunningham et al[1] and the letter by Kotz et al report on similar topics but come from different research traditions. As such, they serve as a good illustration of the strengths and limitations of randomized clinical trial (RCT) and epidemiological survey research methods and can highlight the synergistic benefits of employing multiple different research methods exploring the same topic.

The strength of the RCT method used in the trial by Cunningham et al[1] is that it allows for statements of causation, finding that participants who were sent the nicotine patches (along with a letter) were more likely to report quitting smoking compared with participants not sent the nicotine patches. The letter by Kotz et al points out several valid limitations. Primarily, the steps taken to recruit the participants resulted in a sample that was not representative, making it important to be cautious as to whether the same outcomes would occur in the general population of smokers.

The letter by Kotz et al references a cross-sectional study[2] and a prospective cohort study[3] that indicate, while prescribed nicotine replacement therapy (NRT) is associated with increased tobacco cessation rates, NRT purchased over-the-counter (OTC) is not. The strength of these surveys is that they provide a fairly accurate snapshot of what is actually going on in the general population of smokers. The limitation of the studies is that the results cannot be used to make causal statements about whether it is the NRT or another systematic difference between those who get their NRT through prescription vs OTC (and those who try to quit without using NRT at all) that leads to the observed findings.

The real strength of a cumulative research endeavor is observed when these studies are examined together. The articles referenced by Kotz et al[2,3] note the lack of relation between NRT purchased OTC and increased rates of tobacco cessation. One possible explanation for this lack of observed effect is that NRT provided by prescription may be accompanied by behavioral support but that NRT purchased OTC is not. The article by Cunningham et al[1] partially addresses this possible explanation, indicating that NRT without behavioral support can increase tobacco cessation rates. This leads to an accumulation of evidence and helps narrow the range of possible explanations regarding why people purchasing an OTC NRT may be no more likely to have increased tobacco cessation rates than people who attempt to quit without using NRT at all. This narrowing of possibilities then brings into focus research questions regarding the potential effect of OTC NRT as a means of promoting tobacco cessation in the general population. That is, if it is not the behavioral support that differentiates the observed differential effect between NRT when provided as a prescription vs when purchased OTC, then what else is going on and what can be done to promote the impact of OTC NRT? These questions would benefit from the participation of other research traditions, such as those specializing in qualitative methods, to shed light on this intriguing issue and to generate hypotheses that can then be tested using RCT and epidemiological surveys.

John A. Cunningham, PhD

Author Affiliations: Centre for Addiction and Mental Health, Toronto, Canada (Cunningham); University of Toronto, Toronto, Canada (Cunningham).

Corresponding Author: John A. Cunningham, PhD, Centre for Addiction and Mental Health, 33 Russell St, Toronto, ON M5S 2S1, Canada (john.cunningham@camh.ca).

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LESS IS MORE

Estimating Vitamin D Status and the Choice of Supplementation Dose

To the Editor In a recent issue of *JAMA Internal Medicine*, Bischoff-Ferrari and colleagues[1] reported the results of an interesting randomized clinical trial testing the efficiency of physiological (equivalence, 800 IU/d) and supraphysiological doses (equivalence, 2000 IU/d or 800 IU/d plus calcifediol 300 µg/mo) of vitamin D supplements in lowering the risk of functional decline. The authors found that older participants in the higher-dose vitamin D groups experienced the greater incidence of falls,[1] a result already described with mega doses of vitamin D supplementation[2] but in contradiction with the well-recognized antifall effect of physiological doses.[3]

Before claiming that high-dose vitamin D supplementation makes seniors fall, we wish to draw attention to the secondary analyses stratified by initial vitamin D status.[1] The 12-month number of falls was greater after high-dose vs low-dose vitamin D supplementation only in the group that had no hypovitaminosis D at baseline (ie, 25-hydroxyvitamin D [25(OH)D] ≥ 20 ng/mL [to convert 25[OH]D level to nanomoles per liter, multiply by 2.496]), but not in the group with initial hypovitaminosis D less than 20ng/mL (P = .03 and P = .33, respectively). It thus appears that, among people without hypovitaminosis D, high-dose vitamin D supplementation, aimed at increasing 25(OH)D concentration to supraphysiological levels, is probably not useful—and might be toxic—compared with lower doses aiming at preventing hypovitaminosis D and maintaining 25(OH)D concentration to physiological levels.

These data confirm the current hypothesis of a possible U-shaped or J-shaped effect of vitamin D, with both low and high 25(OH)D concentrations being associated with adverse health events.[4] For this reason, we call for the need to determine older individuals' vitamin D status before any vitamin D supplementation. However, we recognize that such systematic screening for hypovitaminosis D is currently compromised in this population due to the cost of 25(OH)D assay, which is higher than the annual supplementation. To avoid the current trend toward universal supplementation on sight, and to help determining which individuals should receive lower-dose or higher-dose vitamin D supplements, it is urgently needed to develop new cost-effective routine screening strategies to provide an appropriate medical decision. For instance, we recently developed a clinical tool able to identify older adults with hypovitaminosis D who may be administered high-dose supplements without blood test.[5] Further investigations will be necessary to examine the feasibility, cost-effectiveness, and usefulness of such tools in daily practice and to estimate if they allow supplementing older adults in a personalized way, thus avoiding vitamin D toxic effects described by Bischoff-Ferrari and colleagues.

Cédric Annweiler, MD, PhD
Guillaume Duval, MD, MS
Cyrille P. Launay, MD, PhD

Author Affiliations: Division of Geriatric Medicine, Department of Neuroscience, Angers University Hospital, UPRES EA 4638, University of Angers, UNAM, Angers, France (Annweiler, Duval); Service of Geriatric Medicine and Geriatric Rehabilitation, Department of Medicine, Lausanne University Hospital, Switzerland (Launay).

Corresponding Author: Cédric Annweiler, MD, PhD, Division of Geriatric Medicine, University Hospital, F-49933 Angers, France (CeAnnweiler@chu-angers.fr).

Conflict of Interest Disclosures: None reported.

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In Reply We agree that high-dose monthly vitamin D is not necessarily harmful among seniors with vitamin D deficiency. However, everyone treated with 24 000 IU vitamin D per month (equivalent to 800 IU/day) achieved the replete range of above 20 ng/mL 25(OH)D (to convert 25[OH]D level to nanomoles per liter, multiply by 2.496), with none reaching a 25(OH)D level above 45 ng/mL.[1] The group treated with 24 000 IU per month included 59.7% of participants with deficient 25(OH)D starting levels less than 20 ng/mL and 40.3% with replete 25(OH)D starting levels greater than 20 ng/mL (range, 20.1-43.5 ng/mL). Thus, at starting levels throughout the wide range of 4.9 to 43.5 ng/mL, 24 000 IU vitamin D per month appears to be effective in safely bringing 25(OH)D levels into what currently appears to be the desirable range for fall prevention.[1] This does not mean that measuring 25(OH)D status is never indicated but suggests that wide spread assessments by serum analysis or algorithm may not be necessary.

Heike A. Bischoff-Ferrari, MD, DrPH
E. John Orav, PhD
Bess Dawson-Hughes, MD

Author Affiliations: Department of Geriatrics and Aging Research, University Hospital Zurich, Switzerland (Bischoff-Ferrari); Centre on Aging and Mobility, University of Zurich, Switzerland (Bischoff-Ferrari); Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts (Orav); USDA Human Nutrition Research Center on Aging, Tufts University, Boston, Massachusetts (Dawson-Hughes).