the subset of UKPDS patients with uncontrolled diabetes and hypertension.[8] The Steno-2 follow-up study found that intensive control of BP, HbA_{1c}, and LDL-C among patients with diabetes and persistent microalbuminuria reduced cardiovascular-related adverse event and death rates 5.5 years after trial completion.[9] It is also possible that resource use declined because GMC patients learned to address health concerns directly with their usual physicians; GMC patients self-reported significantly greater confidence in managing diabetes at the completion of the trial compared with usual care.[2]

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Caffeine Content of Dietary Supplements Consumed on Military Bases

Excessive caffeine consumption, particularly when combined with other stimulants, may increase the risk of hypokalemia, rhabdomyolysis, and other heat-related injuries among athletes and military personnel.[1-3] Caffeine is consumed in a wide range of popular items including coffee, teas, sodas, energy drinks, energy gels, chocolate, gums, and over-the-counter medications. Dietary supplements, which are commonly consumed by military personnel,[4,5] are a poorly characterized source of caffeine. Only with accurate information about the quantity of caffeine in dietary supplements can consumers and clinicians be assured of safe use. As part of an ongoing multidisciplinary collaboration to promote dietary supplement safety, we analyzed some of the most popular supple-

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ments sold on military bases to determine the accuracy of information available to military personnel and their health care providers regarding caffeine content in dietary supplements.

Methods. We identified the most popular dietary supplements sold as capsules (excluding drinks and gels) on military installations labeled as containing either (1) caffeine or (2) 1 or more herbal ingredient known to naturally contain caffeine but without "caffeine" listed on the label. Supplements were purchased at a large, local retail store selling dietary supplements. The quantity of caffeine per serving in the supplements was determined by high-pressure liquid chromatography with UV (HPLC-UV) absorbance after solvent extraction. If the caffeine level was below the limit of quantitation by the HPLC-UV method, liquid chromatography with tandem mass spectrometry detection was used. The results obtained were compared with the caffeine content listed on the product label. All analyses were performed by NSF International.

Results. Thirty-one supplements met our inclusion criteria. Twenty products listed caffeine on the label, and 9 of these products' labels (45%) listed an accurate amount of caffeine (within 10% more or less than the amount listed on the label). Caffeine amounts listed on the label of 5 of the 20 products (25%) varied widely from chromatographically determined levels, with ranges from 27% to 113% of the labeled quantity. Of the 20 products, 6 (30%) listed caffeine as an ingredient without providing an amount on the label. All 6 of these products contained high amounts of caffeine, ranging from 210 to 310 mg per serving.

See Editor's Note at end of letter

Eleven supplement labels listed an herbal ingredient that naturally includes caffeine but did not list "caffeine" on the label. Green tea leaf extract was listed on all 11 labels, with 3 labels also including a second caffeine-containing ingredient (black tea leaf [n=1], white tea leaf extract [n=1], and kola nut [n=1]). Our analyses revealed that these products contained no to minimal amounts of caffeine (range, 0-3 mg of caffeine per serving).

Comment. The law regulating the manufacturing and sales of dietary supplements in the United States has loopholes that allow manufacturers to avoid listing the quantity of caffeine on the label.[6] Our chemical analyses of the caffeine content in dietary supplements popular on military bases found that less than half (9 of 20 [45%]) of the analyzed supplements' labels provided clinically useful information regarding caffeine content. Of the 20 product labels listing caffeine, 5 (25%) failed to meet the minimal legal requirements in that they listed a "per serving" amount of caffeine that was inconsistent with what our analyses detected. In addition, 6 of the 20 product labels (30%) were compliant with legal standards, yet failed to provide clinically useful information about caffeine content even though they each contained more than 200 mg of caffeine per serving. For comparison, soft drinks are prohibited by law to contain more than 71 mg of caffeine per 12 fl oz.

A limitation of our study was that we tested only 1 sample of each supplement. Future research would need to determine if our findings are representative and if caffeine content varies from one sample to another. However, our findings are consistent with prior research demonstrating that commercially available dietary supplement labels do not provide sufficient information in respect to caffeine content.[7,8]

Given the lenient legal framework and inaccurate labels, military personnel are unable to determine if a supplement can be safely combined with other products or foods containing caffeine. This is of increasing concern, as caffeine intake in the form of energy drinks has significantly increased over the past decade, and a recent Centers for Disease Control and Prevention study found that 45% of service members consume energy drinks on a daily basis.[9] In addition, physician reports of adverse reactions are a cornerstone of monitoring supplement safety in the United States, but even after careful review of the label, clinicians are unable to determine if an adverse reaction may be associated with the caffeine contained in an individual supplement. To ensure consumer safety, accurate information on caffeine content should be provided on all dietary supplement labels.

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Author Contributions: Dr Cohen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Cohen, Stevens, and Deuster. *Acquisition of data:* Attipoe, Travis, and Deuster. *Analysis and interpretation of data:* Cohen, Attipoe, Travis, and Deuster. *Drafting of the manuscript:* Cohen, Attipoe, and Stevens. *Critical revision of the manuscript for important intellectual content:* Cohen, Attipoe, Travis, and Deuster. *Statistical analysis:* Cohen and Attipoe. *Obtained funding:* Deuster. *Administrative, technical, and material support:* Cohen, Attipoe, Travis, and Deuster. *Study supervision:* Cohen and Deuster.
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nization that developed the US national standards for dietary supplements. Some of NSF Internationals clients are dietary supplement manufacturers.

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EDITOR'S NOTE

Insufficient Information About Caffeine in Supplements Makes Me Jittery

Recent media reports of deaths related to consumption of drinks high in caffeine[1] remind us that substances that are safe and even beneficial at usual doses (how many of us would have survived residency without caffeinated beverages?) may be harmful when consumed to excess. As demonstrated by the authors of this provocative Research Letter, consumers cannot be certain how much caffeine they are consuming in dietary supplements. The authors tested 20 different supplements sold at military installations: 5 had levels very different from what was advertised on the label, and 6 did not even state on the label the amount of caffeine in the product. This report contributes to other reports in this journal[2] and other journals indicating that to protect the public we need tighter regulation of dietary supplements.

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COMMENTS AND OPINIONS

DMAA as a Dietary Ingredient

DMAA (1,3-dimethylamylamine) is an aliphatic amine added to some dietary supplement (DS) products. We are responding to the Research Letter by Cohen,[1] in which he discussed natural occurrence of DMAA, as well as labeling it a potent "amphetamine derivative" linked in case reports and the news media to adverse cardiovascular toxic effects. We would like to offer the following points in the interest of moving forward the discussion of the health effects of DMAA within the context of sound toxicological and risk assessment principles.

We begin by correcting the assertion by Cohen[1] that DMAA is an amphetamine derivative. DMAA is not synthesized from amphetamine or amphetamine-like compounds, nor does it possess a terminal benzyl constituent found in amphetamine and catechols that is needed to induce specific neurotransmitter release cascades, in addition to providing adrenergic neuronal stimulation.

Cohen[1] cited a Health Canada review that concluded there is no credible evidence of DMAA as a plant constituent. However, other studies not considered by Health Canada have reported confirmation of the presence of DMAA in the geranium plant (68-496 ng/g, Fleming et al[2]) and oil (14 ppb–13 ppm, Li et al[3]).

Cohen[1] discussed DMAA hazards by referencing case studies but did not consider the dose response for DMAA or multiple published clinical studies of the effects from DMAA intake levels recommended by a DS manufacturer. He cited cases of DMAA abuse that presented with cardiovascular pathologic conditions involving unknown or higher than DS label–recommended levels of DMAA consumption. Cohen[1] mentioned 1 of 6 published clinical trials of volunteers consuming DMAA-containing products for up to 10 weeks[4] but did not note that increases in observed blood pressure were approximately 15% above resting baseline levels and transient. None of the adverse effects reported in the case studies occurred during this or any of the other 5 clinical studies involving subjects consuming DMAA. The clinical studies also reported clinical chemical, hematologic, urinalysis, and metabolic panels indicating no effect on liver and renal function after extended use at recommended intake levels. Any discussion on the safety of DMAA in particular and DS in general is informative only if appropriate data weighting is used when comparing controlled experimental exposure studies with case reports of questionable estimates of DS intake. The call by Cohen[1] for immediate recall of all DMAA-containing products is not based on data analysis using sound principles of risk assessment.

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