RESEARCH
Research Paper

Adverse Effects Associated with Multiple Categories of Dietary Supplements: The Military Dietary Supplement Use Study

Joseph J. Knapik, ScD; Daniel W. Trone, PhD; Ryan A. Steelman, MPH; Emily K. Farina, PhD, RD; Harris R. Lieberman, PhD

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ABSTRACT

Background About 50% of Americans and 70% of US military service members (SMs) regularly use dietary supplements (DSs) and some are associated with adverse effects (AEs). SMs are more likely to use unsafe DSs than civilians.

Objective The aim of this investigation was to examine the prevalence of, and factors associated with, AEs.

Design Cross-sectional.

Participants A stratified random sample of 200,000 US SMs from the Air Force, Army, Marine Corps, and Navy were obtained from military workforce records. Eighteen percent (n = 26,681) of successfully contacted SMs (n = 146,365) volunteered to participate between December 2018 and August 2019. Participants completed a detailed online questionnaire on demographic characteristics, lifestyle factors, and AEs associated with DS use.

Main outcome measure Prevalence of, and factors associated with, AEs among DS users.

Statistical analysis Prevalence of AEs was calculated by DS categories. Linear trends, χ^2 statistics, and multivariable logistic regression examined associations between AEs and demographic characteristics, lifestyle factors, and number DSs consumed.

Results Proportion of DS users ($\geq$ 1 time /week) reporting $\geq$1 AE was 18% overall, 20% for combination products (ie, weight loss, muscle building, and before/after workout supplements), 8% for purported prohormones, 6% for protein/amino acid products, 6% for multivitamin/multiminerals, 6% for individual vitamins/minerals, 4% for herbal products, and 2% for joint health products. Combination products are very popular in military personnel with nearly half of SMs regularly taking them. In multivariable analysis, reporting AEs were independently associated with female gender, younger age, higher body mass index, smoking, higher alcohol intake, service in the Army, Navy, or Marine Corps (compared with Air Force), and consumption of a greater number of DSs.

Conclusions A large proportion of SMs report experiencing AEs, especially users of combination products and purported prohormone supplements. This study presents contemporary data collected from a very large at-risk population on potentially hazardous categories of DSs.

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DIETARY SUPPLEMENTS (DSS) ARE COMMERCIALLY available products consumed as an addition to the usual diet and include vitamins, minerals, amino acids, herbs (botanicals), and a variety of other products.[1] The Dietary Supplement Health and Education Act of 1994[1] established the regulatory framework for DSs in the United States. Under the Dietary Supplement Health and Education Act, the Food and Drug Administration (FDA) has limited authority to regulate DSs. Manufacturers must notify the FDA 75 days before marketing a new DS, but FDA approval is not required for retailing a DS product. The FDA has the burden of demonstrating a specific product is unsafe either in the pre- or post-marketing phase before they can take action, although since 2007 manufacturers are required to notify the FDA when serious adverse effects (AEs) are reported to them.[2] However, it is estimated that only 2% of AEs experienced by consumers are reported.[3]

The FDA has banned or warned consumers about specific DS products in the past[4-6] and case reports and case series of AEs associated with DSs are common among US military service members (SMs)[7-10] and civilians.[11-14] DS consumers may experience AEs because of excessive intake, allergic reactions to ingredients, poor quality control in production resulting in contamination, interactions with prescribed

medications, dangerous compounds present in the DS, and/or the inclusion of unlisted or illegal compounds.[15-18] However, self-reported AEs might also result from symptoms that are not related to DS intake.

There have been two prior studies of AEs among military DS users,[19,20] but these used different methods for recruiting participants, different procedures for collecting self-reported AE data, and analyzed the data in considerably different ways. The purpose of this study was to conduct a large, comprehensive examination of AEs experienced by DS users in all US military services, identify potentially dangerous categories of DSs, and examine demographic and lifestyle factors associated with AEs.

RESEARCH SNAPSHOT

Research Question: What is the prevalence of adverse effects reported by US military dietary supplements users? What demographic and lifestyle factors are associated with these adverse effects?

Key Findings: Adverse effects ($\geq$ 1) were reported by 20% of combination product users (ie, weight loss, muscle building, and before/after workout supplements), 8% of purported prohormone users, 6% of protein/amino acid users, 6% of multivitamin/multimineral users, 6% of individual vitamins/mineral users, 4% of herbal users, and 2% of joint health product users. Higher adverse effects reporting was associated with female gender, younger age, higher body mass index, smoking, higher alcohol intake, and consuming more supplements.

MATERIALS AND METHODS

This study was a cross-sectional survey of a stratified random sample of US active duty military SMs. The Naval Health Research Center's Institutional Review Board approved the study protocol and participants signed an informed consent document. Investigators adhered to policies and procedures for protection of human subjects as prescribed by Department of Defense Instruction 3216.01 and the research was conducted in adherence with provisions of 32 Code of Federal Regulations Part 219.

Sampling Frame

Details of the sampling frame, solicitation of SMs, subject flow through the study, sample size determination, number of participants by demographics and lifestyle factors, and response bias have been previously reported.[21] Briefly, the Department of Defense's Defense Manpower Data Center provided a list of a random sample of 200,000 active duty SMs stratified by sex (88% male and 12% female) and branch of service (Army 36%, Air Force 24%, Marines 15%, and Navy 25%), based on military demographics as of June 2018. Recruitment of SMs from this random sample into the study involved a maximum of 12 contacts with each SM. The prospective participant was initially sent an introductory postal letter with a $1 incentive to increase response rate.[22,23] The letter described the survey, included a link to a secure website, and provided a unique login that could be used to access the survey and electronically sign the consent form. A follow-up e-mail message after 10 days and postcard after 3 weeks was sent as a reminder to those who did not initially complete the survey. If no response was received after sending the postcard, the subsequent contacts included up to seven e-mail messages and three postcard reminders evenly distributed over 8 months, after which contact with the SM ended. Responders were taken off the distribution list, so the reminders were sent only to those who did not respond. Recruitment began in December 2018, and no further recruitment was conducted or surveys accepted after August 2019.

Survey Description

The questionnaire was designed to: describe participants, obtain types and frequency of DSs used in the past 6 months, and determine AEs associated with DSs. To comprehensively describe participants, there were questions on demographic characteristics (eg, gender, age, education, height, and weight), lifestyle characteristics (eg, amount of exercise, tobacco use, and alcohol consumption), and military service branch. Supplement use questions included 96 generic DSs (eg, multivitamins/multiminerals [MVM], individual vitamins and minerals, proteins/amino acids [AAs], and herbal products) and 67 brand-name products. The brand-name products listed were included in many previous Armed Forces DS surveys,[20,24-26] but were updated based on a review of DSs sold in the Army, Marine Corps, and Air Force Exchange Systems as well as General Nutrition Center stores on or near military installations. There were also open text fields on the questionnaire where SMs could include supplements not on the provided lists. SMs indicated whether or not they used a particular generic or specific DS, their frequency of use, and if believed they experienced any specific AE due to consuming that DS. For frequency of use there were five response categories, including "never," "once a month," "once a week," "2 to 6 times/week," or "daily." AEs on the questionnaire were called "side effects," and a list of AEs was located alongside each DS. The AE list included symptoms related to cardiovascular, gastrointestinal, muscular, sleep disturbance, and neurological symptoms. Specific symptoms listed on the questionnaire included "palpitations, racing heart," "abdominal pain," "nausea/vomiting," "diarrhea," "muscle cramps/pain/weakness," "sleep disturbances/insomnia," "dizzy/confusion/lightheaded," "tingling/numb in extremities," "seizures/convulsions/tremors," and "other." If "other" was selected, a space was provided to explain the experienced AE. Table 1 provides DS category definitions used in this study.

Data Analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences.[27] For each of the 163 listed DSs, users were defined as those who reported consuming the DS $\geq$ 1/week (ie, responded "once a week," "2 to 6 times/week," or "daily" for that DSs). Body mass index (BMI) was computed from the questionnaire responses as weight in kilograms / height in meters^2. Weekly duration of aerobic and resistance training (minutes per week) was calculated by multiplying reported weekly exercise frequency (sessions per week) by the reported duration of training (minutes per session). Alcohol consumption was quantified under the

Table 1. Prevalence of adverse effects (AEs) by dietary supplement category reported by a representative cohort of service members in the US Military Dietary Supplement Study

Category	Palpitations, Racing Heart	Abdominal Pain	Nausea, Vomiting	Diarrhea	Muscle Cramps, Pain, Weakness	Sleep Disturbances, Insomnia	Dizzy, Confused, Lightheaded	Tingling, Numbness	Seizures, Convulsions, Tremors	Other	≥ 1 AEs in Dietary Supplement Category
	← % ± *standard error (n)* →										
Combination product (n = 11,844)	9.3 ± 0.3 (1,103)	2.1 ± 0.1 (251)	2.3 ± 0.1 (268)	4.6 ± 0.2 (546)	1.1 ± 0.1 (134)	5.4 ± 0.2 (645)	2.8 ± 0.2 (327)	6.9 ± 0.2 (813)	0.5 ± 0.1 (60)	2.9 ± 0.2 (347)	20.0 ± 0.4 (2,371)
Purported prohormone (n = 1,299)	1.4 ± 0.3 (18)	1.3 ± 0.3 (17)	1.2 ± 0.3 (15)	1.0 ± 0.3 (13)	0.7 ± 0.2 (9)	2.1 ± 0.4 (27)	0.8 ± 0.2 (10)	0.8 ± 0.2 (10)	0.3 ± 0.2 (4)	3.2 ± 0.5 (41)	8.0 ± 0.8 (104)
Protein or amino acid (n = 11,146)	1.1 ± 0.1 (122)	0.9 ± 0.1 (104)	0.7 ± 0.1 (74)	2.2 ± 0.1 (245)	0.3 ± 0.1 (39)	0.8 ± 0.1 (90)	0.4 ± 0.1 (45)	0.8 ± 0.1 (89)	0.1 ± 0.0 (11)	1.7 ± 0.1 (195)	6.3 ± 0.2 (707)
Multivitamin/ multimineral (n = 11,886)	1.2 ± 0.1 (140)	0.9 ± 0.1 (109)	1.4 ± 0.1 (172)	1.0 ± 0.1 (114)	0.6 ± 0.1 (73)	1.4 ± 0.1 (164)	0.6 ± 0.1 (70)	0.7 ± 0.1 (88)	0.1 ± 0.0 (9)	1.6 ± 0.1 (190)	6.0 ± 0.2 (718)
Individual vitamin or mineral (n = 8,226)	0.8 ± 0.1 (69)	08 ± 0.1 (78)	0.9 ± 0.1 (78)	1.1 ± 0.1 (87)	0.6 ± 0.1 (50)	0.8 ± 0.1 (62)	0.5 ± 0.1 (44)	0.6 ± 0.1 (52)	0.1 ± 0.0 (12)	2.0 ± 0.2 (166)	5.6 ± 0.3 (463)
Herbal substance (n = 5,332)	0.8 ± 0.1 (45)	0.7 ± 0.1 (39)	0.5 ± 0.1 (28)	1.0 ± 0.1 (55)	0.2 ± 0.1 (10)	0.7 ± 0.1 (37)	0.4 ± 0.1 (21)	0.2 ± 0.1 (13)	0.1 ± 0.0 (3)	1.7 ± 0.2 (89)	4.3 ± 0.3 (231)
Joint health product (n = 2,514)	0.1 ± 0.1 (2)	0.3 ± 0.1 (8)	0.2 ± 0.1 (4)	0.5 ± 0.1 (12)	0.3 ± 0.1 (7)	0.2 ± 0.1 (5)	0.0 ± 0.0 (1)	0.1 ± 0.1 (3)	0.0 ± 0.0 (0)	1.0 ± 0.2 (25)	2.0 ± 0.3 (51)
Other (n = 8,177)	0.2 ± 0.1 (17)	0.3 ± 0.1 (26)	0.3 ± 0.1 (28)	0.4 ± 0.1 (35)	0.1 ± 0.0 (9)	1.1 ± 0.1 (88)	0.5 ± 0.1 (38)	0.2 ± 0.0 (15)	0.0 ± 0.0 (1)	1.4 ± 0.1 (118)	3.7 ± 0.2 (299)
Combined AEs (n = 19,731)	6.7 ± 0.7 (1,325)	2.6 ± 0.7 (511)	2.9 ± 0.7 (574)	4.7 ± 0.7 (920)	1.4 ± 0.7 (276)	4.6 ± 0.7 (917)	2.5 ± 0.7 (492)	4.9 ± 0.7 (975)	0.4 ± 0.7 (84)	4.5 ± 0.7 (897)	

Category!	Definition!
Dietary Supplement	Any substance defined by the DSHEA[a]
Multivitamin/Multimineral	DS[b] containing two or more vitamins and/or two or more minerals with no additional supplement ingredients
Protein or Amino Acid	Amino acid mixtures, protein powders, and similar products where the intent is to provide a single or complex protein source
Individual Vitamin or Mineral	DS[b] that is a single vitamin or mineral supplement, such as vitamin D or calcium!
Herbal Supplement	DS[b] that includes one or more herbal ingredients with no nutrient or other supplement ingredient. Also includes plant-derived ingredients.
Purported Prohormone	Steroidal hormone or herbal substitute for hormones marketed as a DS and included the Supplement Facts panel on the label.
Combination Product	DS[b] with mixtures of ingredients from any of the above categories including two or more categories and multiple ingredients. Includes products marketed as weight loss, pre- or post-workout supplements, and muscle/body building products.
Joint Health Product	Substance that purports to improve the functioning of body joints such as glucosamine (with or without chondroitin) or methylsulfonylmethane!
Other Dietary Supplement	Other DS[b] that do not fit into the categories above

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Figure. Figure 1. Dietary Supplement Categories and Definitions of These Categories in the US Military Dietary Supplement Study

assumption that a "standard drink" contained 17.7 mL alcohol.[28] "Standard drinks" included 12 oz regular beer or fermented fruit drink (5% alcohol), 8.5 oz higher-alcohol beer (7% alcohol), 5 oz wine (12% alcohol), 4 oz fortified wine (15% alcohol), and 1.5 oz of liquor (40% alcohol). Supplements and AEs that SMs placed in the "other" categories were individually examined and responses placed into their appropriate categories.

Table 2. Proportion of dietary supplement users reporting adverse effects by number of dietary supplements consumed (≥1 time/wk) in a representative cohort of service members in the US Military Dietary Supplement Study

Adverse effect	1-2 Dietary Supplements (n = 5,303)	3-4 Dietary Supplements (n = 3,741)	≥ 5 Dietary Supplements (n = 10,687)	Risk ratio (95% CI)[a]	*P* value[b]	*P* value[c]
	←——% ± *standard error (n)*——→					
Palpitations, racing heart	3.1 ± 0.2 (166)	5.0 ± 0.4 (187)	9.1 ± 0.3 (972)	2.91 (2.47-3.41)	< 0.01	< 0.01
Abdominal pain	1.1 ± 0.1 (59)	2.1 ± 0.2 (80)	3.5 ± 0.2 (372)	2.48 (1.96-3.13)	< 0.01	< 0.01
Nausea, vomiting	1.5 ± 0.2 (82)	2.2 ± 0.2 (83)	3.8 ± 0.2 (409)	2.48 (1.96-3.13)	< 0.01	< 0.01
Diarrhea	2.0 ± 0.2 (104)	3.6 ± 0.3 (133)	6.4 ± 0.2 (683)	3.26 (2.66-4.00)	< 0.01	< 0.01
Muscle cramps, pain, weakness	0.5 ± 0.1 (29)	1.0 ± 0.2 (39)	1.9 ± 0.1 (208)	3.56 (2.42-5.24)	< 0.01	< 0.01
Sleep disturbances, insomnia	2.1 ± 0.2 (113)	3.4 ± 0.3 (129)	6.3 ± 0.2 (675)	2.96 (2.44-3.61)	< 0.01	< 0.01
Dizzy, confused, lightheaded	1.2 ± 0.1 (65)	1.7 ± 0.2 (62)	3.4 ± 0.2 (365)	2.79 (2.15-3.62)	< 0.01	< 0.01
Tingling, numbness	1.8 ± 0.2 (98)	3.3 ± 0.3 (124)	7.0 ± 0.2 (753)	3.81 (3.10-4.69)	< 0.01	< 0.01
Seizures, convulsions, tremors	0.0 ± 0.0 (2)	0.3 ± 0.1 (10)	0.7 ± 0.1 (72)	17.86 (4.39-72.77)	< 0.01	< 0.01
Other	2.5 ± 0.2 (132)	4.1 ± 0.3 (152)	5.7 ± 0.2 (613)	2.30 (1.92-2.77)	< 0.01	< 0.01
Individuals reporting ≥ 1 adverse effects	10.3 ± 0.4 (546)	16.0 ± 0.6 (600)	23.3 ± 0.4 (2,486)	2.26 (2.07-2.46)	<0.01	<0.01

[a] ≥ 5 per week/1 to 2 per week.
[b] Based on χ^2 test.
[c] Linear trend.

Table 3. Prevalence of adverse effects among dietary supplement category (DS[a]) users (≥ 1 times/wk) by demographic and lifestyle characteristics in a representative cohort of service members in the US Military Dietary Supplement Study

Variable	Strata	Any DS[a] Users	Combination Product Users	Purported Pro-hormone Users	Protein/ Amino Acid Users	MVM[b] Users	Individual Vitamin/ Mineral Users	Herbal Users	Joint Health Product Users	Other DS[a] Users
		% ± *standard error*								
Gender	Male	17.9 ± 0.3	19.4 ± 0.4	8.0 ± 0.8	5.9 ± 0.2	5.6 ± 0.2	4.9 ± 0.3	4.2 ± 0.3	1.9 ± 0.3	3.6 ± 0.2
	Female	21.3 ± 0.8	24.3 ± 1.1	10.0 ± 3.1	9.1 ± 0.8	8.3 ± 0.6	8.7 ± 0.7	4.6 ± 0.6	2.5 ± 0.8	3.9 ± 0.6
	P value[c]	< 0.01	< 0.01	0.68	< 0.01	< 0.01	< 0.01	0.57	0.49	0.58
Age (y)	18-24	20.8 ± 0.7	21.7 ± 0.9	9.6 ± 2.2	7.0 ± 0.6	6.3 ± 0.6	5.1 ± 0.6	3.5 ± 0.7	2.3 ± 1.1	4.7 ± 0.6
	25-29	18.6 ± 0.6	19.5 ± 0.8	6.9 ± 1.7	5.8 ± 0.4	5.9 ± 0.5	5.1 ± 0.5	3.8 ± 0.6	1.4 ± 0.6	2.6 ± 0.4
	30-39	18.3 ± 0.4	20.1 ± 0.6	8.1 ± 1.1	6.4 ± 0.4	5.5 ± 0.3	5.8 ± 0.4	4.5 ± 0.4	1.6 ± 0.4	3.3 ± 0.3
	≥ 40	16.7 ± 0.6	18.8 ± 0.9	8.0 ± 1.5	5.6 ± 0.6	7.2 ± 0.5	6.1 ± 0.6	5.0 ± 0.6	3.2 ± 0.7	4.7 ± 0.5
	P value[c,d]	< 0.01/< 0.01	0.13/0.06	0.80/0.75	0.22/0.21	0.04/0.35	0.51/0.15	0.32/0.06	0.07/0.11	< 0.01/0.48
Education	Some HS[e]/HS graduate	19.7 ± 0.8	20.1 ± 1.0	8.8 ± 2.0	7.1 ± 0.6	6.9 ± 0.7	6.5 ± 0.8	4.5 ± 0.9	2.7 ± 1.2	4.0 ± 0.6
	Some college	20.3 ± 0.4	21.0 ± 0.5	7.7 ± 1.1	6.9 ± 0.4	6.8 ± 0.4	5.7 ± 0.4	3.9 ± 0.4	2.0 ± 0.4	3.7 ± 0.3
	College degree	16.1 ± 0.4	18.9 ± 0.6	8.0 ± 1.2	5.2 ± 0.3	5.2 ± 0.3	5.3 ± 0.4	4,6 ± 0.4	1.9 ± 0.4	3.4 ± 0.3
	P value[c,d]	< 0.01/< 0.01	0.03/0.07	0.89/0.82	< 0.01/< 0.01	< 0.01/< 0.01	0.41/0.19	0.48/0.52	0.80/0.58	0.63/0.34
Body mass index	< 25.0	16.5 ± 0.5	18.6 ± 0.7	11.1 ± 2.2	6.5 ± 0.5	5.2 ± 0.4	5.7 ± 0.5	3.5 ± 0.5	1.9 ± 0.6	4.3 ± 0.4
	25.0-29.9	18.7 ± 0.4	20.2 ± 0.5	6.3 ± 0.9	6.2 ± 0.3	6.1 ± 0.3	5.2 ± 0.3	4.3 ± 0.4	2.2 ± 0.4	3.5 ± 0.3
	≥ 30.0	20.7 ± 0.7	21.5 ± 0.9	8.9 ± 1.5	6.5 ± 0.6	6.9+0.5	6.8 ± 0.6	5.3 ± 0.7	1.0 ± 0.4	3.2 ± 0.5
	P value[c,d]	< 0.01/< 0.01	0.04/0.01	0.05/0.61	0.83/0.93	0.04/0.01	0.07/0.23	0.09/0.03	0.25/0.30	0.20/0.09
Aerobic exercise duration (min/wk)	≤ 90	19.0 ± 0.5	21.2 ± 0.7	7.0 ± 1.5	6.9 ± 0.5	5.5 ± 0.4	5.8 ± 0.5	5.2 ± 0.6	2.4 ± 0.6	4.3 ± 0.4
	91-180	17.6 ± 0.5	21.1 ± 0.8	9.3 ± 1.7	5.9 ± 0.5	5.5 ± 0.4	5.1 ± 0.5	3.6 ± 0.5	1.1 ± 0.4	3.3 ± 0.4
	181-300	18.1 ± 0.6	19.1 ± 0.8	8.5 ± 1.6	5.6 ± 0.5	6.2 ± 0.5	5.6 ± 0.5	4.1 ± 0.6	2.8 ± 0.7	3.4 ± 0.4
	> 300	18.8 ± 0.6	18.8 ± 0.7	7.6 ± 1.3	6.6 ± 0.4	7.0 ± 0.5	5.9 ± 0.5	4.3 ± 0.5	1.9 ± 0.5	3.5 ± 0.4
	P value[c,d]	0.23/0.98	0.02/<0.01	0.75/0.94	0.17/0.57	0.07/0.01	0.65/0.70	0.23/0.42	0.20/0.98	0.32/0.24
Resistance training duration (min/wk)	≤ 45	17.1 ± 0.5	21.9 ± 0.9	7.2 ± 2.1	7.3 ± 0.7	7.6 ± 0.5	6.4 ± 0.5	5.1 ± 0.6	2.0 ± 0.7	5.4 ± 0.6
	46-135	16.4 ± 0.6	20.6 ± 0.9	9.8 ± 2.3	5.3 ± 0.5	5.3 ± 0.4	5.3 ± 0.5	3.9 ± 0.6	1.8 ± 0.6	3.5 ± 0.5
	136-300	19.1 ± 0.5	19.6 ± 0.7	8.0 ± 1.5	6.3 ± 0.4	5.4 ± 0.4	5.7 ± 0.5	3.8 ± 0.5	2.4 ± 0.6	3.2 ± 0.4
	> 300	20.6 ± 0.6	19.2 ± 0.6	7.7 ± 1.1	6.3 ± 0.4	5.8 ± 0.4	5.1 ± 0.5	4.4 ± 0.5	1.8 ± 0.5	3.0 ± 0.3
	P value[c,d]	< 0.01/< 0.01	0.07/< 0.01	0.80/0.78	0.11/0.80	< 0.01/0.01	0.26/0.10	0.33/0.43	0.84/0.99	< 0.01/< 0.01

(*continued on next page*)

Table 3. Prevalence of adverse effects among dietary supplement category (DS[a]) users (≥ 1 times/wk) by demographic and lifestyle characteristics in a representative cohort of service members in the US Military Dietary Supplement Study (*continued*)

Variable	Strata	Any DS[a] Users	Combination Product Users	Purported Pro-hormone Users	Protein/ Amino Acid Users	MVM[b] Users	Individual Vitamin/ Mineral Users	Herbal Users	Joint Health Product Users	Other DS[a] Users
Smoking	Never smoked	17.0 ± 0.3	18.8 ± 0.5	8.9 ± 1.1	6.0 ± 0.3	5.8 ± 0.3	5.6 ± 0.3	4.3 ± 0.3	2.2 ± 0.4	3.7 ± 0.3
	Smoked but quit	19.7 ± 0.7	20.9 ± 0.8	6.9 ± 1.5	6.3 ± 0.5	6.2 ± 0.5	5.2 ± 0.6	5.5 ± 0.7	1.8 ± 0.6	3.6 ± 0.5
	Smoker	21.7 ± 0.7	23.0 ± 0.9	7.4 ± 1.6	6.9 ± 0.6	6.8 ± 0.6	5.9 ± 0.7	2.9 ± 0.6	1.6 ± 0.6	3.6 ± 0.5
	P value[c]	< 0.01	< 0.01	0.52	0.29	0.21	0.70	0.02	0.70	0.96
Smokeless tobacco use	Never used	17.8 ± 0.3	19.8 ± 0.4	8.4 ± 0.9	6.1 ± 0.3	5.8 ± 0.2	5.7 ± 0.3	4.4 ± 0.3	2.0 ± 0.3	3.6 ± 0.2
	Used but quit	19.5 ± 1.0	20.3 ± 1.2	5.3 ± 1.9	6.9 ± 0.8	5.4 ± 0.7	4.1 ± 0.8	3.4 ± 0.9	0.9 ± 0.6	3.9 ± 0.7
	User	21.2 ± 0.8	21.3 ± 1.0	8.8 ± 1.8	6.5 ± 0.6	7.1 ± 0.7	5.9 ± 0.8	4.6 ± 0.8	3.0 ± 0.9	3.7 ± 0.6
	P value[c]	< 0.01	0.33	0.42	0.47	0.13	0.23	0.60	0.21	0.95
Alcohol intake (mL/wk)	0	16.6 ± 0.5	17.6 ± 0.7	7.3 ± 1.4	6.3 ± 0.4	5.7 ± 0.4	5.9 ± 0.5	4.5 ± 0.5	1.5 ± 0.5	3.7 ± 0.4
	0.23-24.85	17.9 ± 0.6	19.1 ± 0.8	9.1 ± 1.8	6.0 ± 0.5	6.0 ± 0.5	5.9 ± 0.5	3.6 ± 0.5	1.8 ± 0.5	3.5 ± 0.4
	24.86-71.69	18.2 ± 0.6	19.6 ± 0.7	6.8 ± 1.4	6.0 ± 0.4	5.6 ± 0.4	5.2 ± 0.5	3.9 ± 0.5	2.5 ± 0.6	3.3 ± 0.4
	≥ 71.70	21.4 ± 0.6	24.0 ± 0.8	9.0 ± 1.5	6.7 ± 0.5	7.0 ± 0.5	5.3 ± 0.5	5.1 ± 0.6	2.3 ± 0.6	4.0 ± 0.4
	P value[c,d]	< 0.01/< 0.01	< 0.01/< 0.01	0.62/0.60	0.66/0.53	0.08/0.06	0.61/0.25	0.26/0.44	0.54/0.21	0.66/0.68
Service	Air Force	14.7 ± 0.4	16.8 ± 0.6	8.0 ± 1.5	5.4 ± 0.4	4.6 ± 0.3	4.0 ± 0.4	3.1 ± 0.4	1.7 ± 0.4	2.8 ± 0.3
	Army	19.8 ± 0.5	20.3 ± 0.7	6.5 ± 1.1	6.2 ± 0.4	6.2 ± 0.4	6.4 ± 0.5	5.2 ± 0.5	2.2 ± 0.5	3.9 ± 0.4
	Marine Corps	22.3 ± 0.9	23.0 ± 1.0	9.1 ± 2.0	6.8 ± 0.6	7.7 ± 0.7	5.8 ± 0.8	3.9 ± 0.8	2.9 ± 1.0	3.9 ± 0.6
	Navy	20.5 ± 0.6	23.0 ± 0.9	10.3 ± 1.9	7.5 ± 0.6	7.6 ± 0.5	7.2 ± 0.6	4.9 ± 0.6	1.9 ± 0.6	4.5 ± 0.5
	P value[c]	< 0.01	< 0.01	0.28	0.01	< 0.01	< 0.01	0.01	0.63	0.03

[a]DS = dietary supplement.
[b]MVM = multivitamin/multimineral.
[c]Based on χ^2 test.
[d]Based on χ^2 test for trend.
[e]HS = high school.

Prevalence (as a percent) and its standard error were calculated for each AE. Differences across various strata of demographic factors, lifestyle characteristics, and military services were examined with χ^2 statistics. Where variables were ordinal (ie, age, education, BMI, aerobic training duration, resistance training duration, alcohol intake, and number of DSs), Mantel-Haenszel tests for linear trend were also performed. Multivariable logistic regression examined associations between independent variables involving demographic, lifestyle, military characteristics, and number of different DSs consumed and dependent variables that included AEs in each DS category (see the Figure). Logistic regression produced odds ratios and 95% CI reported in the tables. Statistical significance was set at $P < .05$ for all statistics. Some participants did not complete all questions and the number of SMs responding is provided for variables in the Tables.

RESULTS

From the initial sample frame of 200,000 SMs, 73% (n = 146,365) were successfully contacted (ie, no returned postal mail), and of these, 26,681 (18.2%) signed the informed consent and completed the survey.

Prevalence of Self-Reported AEs

Table 1 presents the overall prevalence of AEs reported by SMs in each DS category. The overall proportion of DS users reporting $\geq$ 1 AEs was 18.4% $\pm$ 0.3%. In descending order, AEs were most often reported for combination products, purported prohormones, protein/AAs, MVM, individual vitamins/minerals, herbal substances, other DSs, and joint health products. If combination products and purported prohormones were not included, 10.0% $\pm$ 0.7% of SMs reported $\geq$ 1 AE; if only MVM, individual vitamins/minerals and herbs were included, 6.4% $\pm$ 0.7% of SMs reported $\geq$ 1 AE.

Table 2 presents AEs by the number of DSs consumed and compares the risk of an AE when consuming $\geq$ 5 different DSs per week to that when consuming 1 to 2 different DSs per week. As the number of DSs increased, the prevalence of all types of AEs increased in all DS categories. The risk of an AE was 2.3 to 17.9 times higher among those consuming $\geq$ 5 DSs compared with those consuming 1 to 2 DSs.

Factors Associated with AEs (Univariable Analyses)

Table 3 presents the prevalence of AEs in each DS category by demographic, lifestyle, and military characteristics. Women were more likely than men to report AEs among users of any DS, combination products, protein/AAs, MVM, and individual vitamins/minerals. As age increased, users of any DS were less likely to report AEs and the youngest and oldest were more likely to report AEs among users of MVM and other DSs. SMs with less formal education were more likely to report AEs among users of any DS, combination products, protein/AAs, and MVM. Reporting of AEs increased with an increase in BMI among users of any DSs, combination products, MVM, and herbals. As aerobic exercise duration increased, reporting of AEs decreased for combination product users, but increased for MVM users. As resistance training duration increased, reporting of AEs increased among users of any DS, but decreased among users of combination products, MVM, and other DSs. Smokers and former smokers were more likely to report AEs among users of any DS and combination products; among herbal users, smokers were less likely to report AEs than nonsmokers or former smokers. Smokeless tobacco users or former users were more likely to report AEs for any DS, but not for any of the other DS categories. As alcohol intake increased, reporting of AEs increased for users of any DS and combination products. Among the military services, those serving in the Air Force had the lowest risk of reporting AEs in all DS categories except purported prohormones. Marine Corps and Navy personnel had the highest reporting of AEs among users of any DS, combination products, proteins/AAs, and MVM.

Factors Independently Associated with AEs (Multivariable Analyses)

Table 4 presents multivariable analyses examining the associations between AEs reported by users of each DS category and the demographic factors, lifestyle characteristics, military service, and number of supplements. Among users of any DS, reporting of AEs was higher among women, smokers, and former smokers, and those serving in the Army, Marine Corps, or Navy (compared with the Air Force); reporting decreased as age increased, and reporting increased with an increase in BMI, alcohol consumption, or number of supplements consumed. Among users of combination products, reporting of AEs was higher among women, those with some college, smokers, and those serving in the Army, Marine Corps, or Navy (compared with the Air Force); reporting increased with an increase in BMI, alcohol intake, or number of supplements consumed; reporting generally decreased with an increase in age, aerobic exercise duration, or resistance training duration. None of the variables was independently associated with AEs among purported prohormone users.

Among users of proteins/AAs, reporting of AEs was higher among women, Navy and Army personnel (compared with the Air Force) and increased as the number of DSs consumed increased. Among MVM users, reporting of AEs was higher among women, those with less formal education, and those serving in the Army, Marine Corps, or Navy (compared with the Air Force); reporting increased with an increase in BMI, aerobic training duration, alcohol intake, or number of DSs consumed; reporting decreased as resistance training duration increased. Among individual vitamins/minerals users, reporting of AEs was higher among women and those serving in the Army, Marine Corps, or Navy (compared with the Air Force) and reporting increased as BMI increased. Among herbal substances users, risk of reporting AEs was higher among those serving in the Army (compared with the Air Force); risk was lower in smokers compared with nonsmokers. Among joint health product users, reporting of AEs was higher among women, but was not associated with any other factor. Among users of other DSs, risk of reporting AEs was higher in the Army, Marine Corps, or Navy (compared with the Air Force) and decreased as resistance training duration increased.

DISCUSSION

The present study found that a substantial proportion (18%) of a large random sample of military personnel who use DSs reported experiencing $\geq$ 1 AE over a 6-month period, with

Table 4. Associations of self-reported adverse effects by demographic and lifestyle characteristics among users of specific dietary supplement categories in a representative cohort of service members in the US Military Dietary Supplement Study (Multivariable Logistic Regression)[a]

Variable	Strata	Any DS[b] Users (n = 18,522)	Combination Product Users (n = 11,120)	Purported Prohormone Users (n = 1,221)	Protein/Amino Acid Users (n = 10,630)	Multivitamin/ Multimineral Users (n = 11,165)	Individual Vitamin/ Mineral Users (n = 7,704)	Herbal Users (n = 5,057)	Joint Health Product Users (n = 2,375)	Other DS Users (n = 7,707)
		Odds ratio (95% CI)								
Gender	Male	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Female	1.49 (1.34-1.67)	1.48 (1.29-1.72)	0.98 (0.27-3.50)	1.73 (1.37-2.20)	1.79 (1.46-2.22)	2.09 (1.65-2.65)	1.25 (0.88-1.79)	2.23 (1.00-5.01)	1.07 (0.75-1.52)
Age (y)	18-24	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	25-29	0.81 (0.71-0.92)	0.80 (0.69-0.93)	0.76 (0.35-1.68)	0.84 (0.65-1.09)	0.97 (0.73-1.29)	1.04 (0.71-1.51)	1.00 (0.59-1.72)	0.43 (0.09-1.71)	0.54 (0.35-0.83)
	30-39	0.82 (0.72-0.92)	0.81 (0.70-0.94)	0.99 (0.48-2.03)	1.01 (0.79-1.28)	0.90 (0.67-1.19)	1.32 (0.93-1.87)	1.18 (0.71-1.97)	0.76 (0.22-2.58)	0.71 (0.48-1.04)
	≥ 40	0.76 (0.65-0.88)	0.74 (0.61-0.89)	0.86 (0.37-1.98)	0.90 (0.65-1.23)	1.18 (0.87-1.62)	1.37 (0.92-2.05)	1.19 (0.67-2.10)	2.02 (0.55-7.49)	0.93 (0.60-1.44)
Education	HS[c]/HS graduate	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Some college	1.12 (0.99-1.28)	1.17 (1.00-1.36)	0.92 (0.47-1.79)	1.00 (0.78-1.28)	0.96 (0.73-1.26)	0.79 (0.56-1.11)	0.78 (0.47-1.27)	0.95 (0.29-3.13)	1.10 (0.72-1.66)
	College degree	0.90 (0.78-1.03)	1.04 (0.88-1.23)	0.92 (0.44-1.92)	0.71 (0.76-1.26)	0.67 (0.49-0.90)	0.67 (0.46-0.95)	0.90 (0.54-1.51)	0.52 (0.15-1.85)	0.88 (0.56-1.39)
Body mass index	< 25.0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	25.0-29.9	1.16 (1.05-1.27)	1.16 (1.03-1.31)	0.50 (0.29-0.88)	0.98 (0.81-1.18)	1.25 (1.03-1.53)	1.02 (0.80-1.29)	1.24 (0.88-1.75)	1.16 (0.55-2.44)	0.83 (0.63-1.10)
	≥ 30.0	1.28 (1.13-1.44)	1.26 (1.08-1.45)	0.72 (0.39-1.33)	0.98 (0.76-1.25)	1.37 (1.07-1.75)	1.33 (1.00-1.67)	1.48 (0.98-2.24)	0.39 (0.12-1.28)	0.75 (0.52-1.10)
Aerobic exercise duration (min/wk)	≤ 90	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	91-180	0.95 (0.85-1.06)	0.98 (0.86-1.11)	1.26 (0.66-2.40)	0.87 (0.69-1.09)	1.08 (0.86-1.37)	0.88 (0.66-1.17)	0.67 (0.45-1.00)	0.46 (0.18-1.20)	0.76 (0.54-1.06)
	181-300	0.94 (0.84-1.05)	0.87 (0.76-1.00)	1.22 (0.64-2.33)	0.79 (0.62-1.00)	1.30 (1.02-1.65)	0.97 (0.72-1.30)	0.75 (0.51-1.12)	0.84 (0.37-1.89)	0.81 (0.57-1.15)
	> 300	0.91 (0.81-1.01)	0.87 (0.76-0.99)	1.12 (0.60-2.10)	0.96 (0.77-1.20)	1.55 (1.23-1.96)	1.07 (0.80-1.42)	0.80 (0.54-1.18)	0.75 (0.32-1.77)	0.93 (0.66-1.31)
Resistance training duration (min/wk)	≤ 45	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	46-135	0.92 (0.82-1.04)	0.91 (0.77-1.06)	1.15 (0.49-2.71)	0.74 (0.55-1.00)	0.69 (0.54-0.87)	0.88 (0.66-1.19)	0.83 (0.55-1.23)	1.12 (0.40-3.10)	0.64 (0.45-0.91)
	136-300	0.94 (0.84-1.05)	0.84 (0.72-0.97)	0.85 (0.39-1.87)	0.88 (0.68-1.15)	0.61 (0.48-0.77)	0.96 (0.72-1.29)	0.81 (0.54-1.21)	1.52 (0.60-3.84)	0.59 (0.41-0.84)
	> 300	0.92 (0.81-1.04)	0.79 (0.68-0.92)	0.82 (0.38-1.78)	0.78 (0.60-1.03)	0.56 (0.43-0.72)	0.86 (0.63-1.18)	0.89 (0.58-1.36)	1.26 (0.45-3.55)	0.55 (0.38-0.80)
Smoking	Never smoked	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Smoked but quit	1.12 (1.00-1.24)	1.12 (0.98-1.27)	0.82 (0.44-1.50)	0.95 (0.76-1.18)	1.03 (0.83-1.28)	0.96 (0.72-1.27)	1.30 (0.91-1.86)	0.79 (0.34-1.79)	0.97 (0.70-1.35)
	Smoker	1.23 (1.11-1.37)	1.23 (1.09-1.40)	0.75 (0.42-1.33)	1.10 (0.89-1.36)	1.13 (0.90-1.41)	1.08 (0.81-1.44)	0.63 (0.40-0.99)	0.62 (0.24-1.60)	0.93 (0.66-1.33)

(*continued on next page*)

Table 4. Associations of self-reported adverse effects by demographic and lifestyle characteristics among users of specific dietary supplement categories in a representative cohort of service members in the US Military Dietary Supplement Study (Multivariable Logistic Regression)[a] (*continued*)

Variable	Strata	Any DS[b] Users (n = 18,522)	Combination Product Users (n = 11,120)	Purported Prohormone Users (n = 1,221)	Protein/Amino Acid Users (n = 10,630)	Multivitamin/ Multimineral Users (n = 11,165)	Individual Vitamin/ Mineral Users (n = 7,704)	Herbal Users (n = 5,057)	Joint Health Product Users (n = 2,375)	Other DS Users (n = 7,707)
Smokeless tobacco use	Never used	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Used but quit	1.00 (0.87-1.15)	0.96 (0.81-1.14)	0.54 (0.22-1.33)	1.18 (0.90-1.57)	0.87 (0.63-1.19)	0.83 (0.54-1.28)	0.59 (0.32-1.08)	0.53 (0.12-2.41)	1.09 (0.71-1.69)
	User	1.01 (0.90-1.13)	0.97 (0.84-1.11)	1.15 (0.67-1.98)	1.02 (0.81-1.29)	1.13 (0.88-1.44)	1.10 (0.80-1.52)	1.07 (0.69-1.67)	2.14 (0.95-4.81)	1.05 (0.72-1.52)
Alcohol intake (mL/wk)	0	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	0.23-24.85	1.16 (1.04-1.29)	1.10 (0.96-1.27)	1.24 (0.66-2.34)	0.98 (0.77-1.23)	1.14 (0.91-1.43)	1.01 (0.78-1.32)	0.83 (0.55-1.23)	1.68 (0.64-4.43)	0.97 (0.69-1.36)
	24.86-71.69	1.16 (1.04-1.30)	1.14 (1.00-1.31)	1.05 (0.56-1.97)	1.06 (0.84-1.32)	1.13 (0.90-1.43)	0.97 (0.74-1.28)	0.95 (0.64-1.41)	2.20 (0.90-5.88)	0.94 (0.67-1.32)
	≥ 71.70	1.38 (1.23-1.53)	1.43 (1.25-1.63)	1.27 (0.71-2.26)	1.14 (0.91-1.43)	1.42 (1.13-1.78)	0.97 (0.72-1.29)	1.27 (0.87-1.85)	1.88 (0.70-5.06)	1.08 (0.77-1.51)
Service branch	Air Force	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	Army	1.47 (1.33-1.62)	1.35 (1.19-1.53)	0.89 (0.49-1.60)	1.24 (1.01-1.53)	1.27 (1.03-1.57)	1.70 (1.31-2.21)	1.61 (1.12-2.32)	1.49 (0.67-3.30)	1.56 (1.13-2.16)
	Marine Corps	1.57 (1.38-1.78)	1.59 (1.36-1.85)	1.40 (0.70-2.79)	1.25 (0.96-1.61)	1.65 (1.25-2.17)	1.76 (1.21-2.54)	1.25 (0.73-2.12)	2.02 (0.76-5.37)	1.54 (1.01-2.33)
	Navy	1.49 (1.34-1.65)	1.44 (1.26-1.64)	1.45 (0.78-2.70)	1.42 (1.13-1.77)	1.54 (1.24-1.90)	1.80 (1.37-2.36)	1.43 (0.98-2.09)	1.22 (0.49-3.26)	1.59 (1.14-2.22)
No. of DS Consumed	1-2	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
	2-4	1.64 (1.44-1.86)	1.21 (1.01-1.45)	1.40 (0.70-4.61)	1.73 (1.16-2.59)	1.11 (0.82-1.52)	0.77 (0.52-1.14)	0.75 (0.43-1.29)	0.70 (0.15-3.26)	0.64 (0.41-1.00)
	≥ 5	2.59 (2.32-2.88)	1.33 (1.14-1.55)	1.45 (0.78-2.70)	2.09 (1.46-2.99)	1.67 (1.29-2.15)	0.86 (0.62-1.18)	0.76 (0.49-1.17)	0.71 (0.21-2.44)	0.71 (0.42-1.00)

[a]Models are adjusted for all variables presented in the table: gender, age, education, body mass index, aerobic exercise duration, resistance exercise duration, smoking, smokeless tobacco use, alcohol intake, service branch, and number of supplements consumed per week.
[b]DS = dietary supplement.
[c]HS = high school.

the largest proportion of users reporting AEs for combination products (20%) and prohormones (8%). Reports of all types of AEs increased as the number of DSs consumed increased. In multivariable analysis, reporting AEs among any DS users were independently associated with female gender; younger age; higher BMI; smoking or former smoking; higher alcohol intake; service in the Army, Navy, or Marine Corps (compared with the Air Force); and consumption of a greater number of DSs.

Prevalence of AEs

In previous studies of DS use in military populations, self-reported AEs have been reported by 8% to 29% of SMs surveyed.[19,20,29-34] The 18% reported in this study falls in the middle of this range. In civilian populations, AEs were reported by only 3% to 9% of individuals surveyed.[15,35-37] The difference in AE prevalence between civilian and military studies are likely because civilians primarily use MVM, individual vitamins/minerals, and herbal substances,[35,38,39] whereas SMs frequently report consumption of combination products, prohormones, and protein/AAs.[20,24,26] When only MVM, individual vitamins/minerals, and herbal substances were examined in the present study, only 6% of SMs reported $\geq$ 1 AEs, similar to the prevalence of AEs in civilian studies.

In the current study, the DS category (see the Figure) with the highest incidence of AEs was combination products, which was in agreement with two past military investigations.[19,20] Marine Corps personnel had the highest proportion of reported AEs in the current study, and were the highest users of combination products and consumers of $\geq$ 5 DSs in past investigations.[20,21] Combination products include supplements used for weight loss, pre- and post-workout substances, and DSs purported to increase muscle mass or muscle strength. They can contain a wide variety of substances that have or are claimed to have specific physiological effects (eg, caffeine and nitric oxide agents)[40] and may interact with other substances in DSs or with medications SMs might be taking. For example, in a study involving 2005-2008 National Health and Nutrition Examination Survey, more than one-third of all adults reported concomitant use of prescription medications and DSs; individuals with a clinically diagnosed medical condition were more than two-and-a-half times more likely to concomitantly use prescription medications and DSs compared with those without clinically diagnosed medical conditions.[41] In 2013-2014 National Health and Nutrition Examination Survey data, 49% of DS users were taking common medications that had potential interactions with specific DSs.[16] It has been estimated that 20% of liver injuries in the United States were attributable to DSs during 2013 and 2014 and about half of these were associated with combination products.[42] It is difficult to attribute direct causality to self-reported AEs because self-reports could be incorrectly reported by the individual (eg, due to other causes) and/or have alternative explanations. Nonetheless, the proportion of SMs reporting AEs for combination products was very high and a matter of considerable concern.

As the number of DSs increased, so did the proportion of SMs reporting AEs in all AE categories. This was reported in a previous study of SMs,[19] but the relationship between AEs and number of DSs consumed has not been addressed in studies of civilian populations. As a greater number of DSs are consumed, individuals could be exposed to more potentially unsafe substances, the possibility of interactions among compounds in these supplements increases, and there are more possible interactions with medications individuals may be taking.

Factors Associated with AEs in DS Categories

Female gender was a robust demographic characteristic associated with AEs. Women were more likely to report AEs in most DS categories in both univariable and multivariable analyses. Women typically report more somatic symptoms than men.[43-45] Hypotheses advanced to account for this difference include socialization that encourages women to disclose illness, distress, and discomfort compared with men; differences in brain function and peripheral processing of noxious sensations; greater vigilance and awareness of bodily symptoms; and seeking of more medical attention.[46-50]

More formal education was generally associated with less symptoms reporting for some DS categories in univariable analyses, but these relationships were considerably attenuated in the multivariable analyses. Conversely, higher BMI was associated with more symptoms reporting for any DSs, combination products, MVM, and herbal substances in both univariable and multivariable analyses. The military has strict weight for height and body fat limitations and there are unfavorable career consequences for those exceeding these limitations.[51-54] SMs with higher BMI may believe using combination products marketed as weight loss supplements, and vitamins/minerals, are a way to reduce weight and/or fat to meet military standards and improve overall health. This may increase their exposure to substances in those supplements that may have harmful effects or are perceived as harmful.

In the multivariable analyses, as the amount of resistance training increased, reports of AEs decreased. This was surprising because previous studies have shown that as the amount of resistance training increases, so does the consumption of most DSs, especially combination products.[20,21,55] Thus, more AEs might be expected among SMs who participate in resistance training because they are using more supplements, especially those with more AEs. One hypothesis is that those who participate in resistance training and experienced AEs with a particular DS discontinue use of that product. They search for products that they believe will improve their resistance training performance while not resulting in AEs. Knapik and colleagues[21] previously showed in this same cohort that 44% of SMs used combination products. Some of the extensive use of combination products could be related to the requirement in the military for a high level of physical fitness to assist in the performance of military occupational tasks. Each military service has physical fitness testing requirements,[56] and like the requirement for body weight/body fat described above, SMs who do not pass the testing standards can adverse performance reports and can be discharged from service for repeated failures. Thus, some individuals may use specific combination products because they are marketed to increase physical fitness or physical performance.

Smoking, having been a smoker, and higher alcohol intake were also associated with more symptom reporting for any DS and combination products. Numerous interactions have been described between alcohol, cigarette smoke, and other substances.[57,58] For example, cigarette smoke is a heterogeneous aerosol containing at least 3,800 constituents in both particulate and gaseous form. The gaseous phase contains carbon dioxide, carbon monoxide, nitrogen oxides, ammonia, hydrogen cyanide, hydrazine, formaldehyde, acetone, and aerolein. Substances in the particulate phase include nicotine, toluene, phenol, and catechol. Carbon dioxide, nicotine, and carbon monoxide are by far the major components of cigarette smoke.[59,60] Nicotine is a bioactive substance that increases circulating norepinephrine, epinephrine, vasopressin, growth hormone, cortisol, adrenocorticotropic hormone, and beta-endorphins[61,62] that could interact with substances in DSs, especially combination products that contain multiple ingredients.

Air Force personnel reported the lowest prevalence of AEs among all the military services for most DS categories. This is likely because among all the services, Air Force personnel were among those with lowest use of combination products and purported prohormones,[21] which were the two categories that had the highest incidence of AEs in the current study. Marine Corps personnel had the highest overall self-reporting of AEs and Knapik and colleagues[21] previously showed in this same cohort that Marine Corps personnel had the highest use of combination products and second highest use of prohormones.

Strengths and Limitations

The questionnaire used in the current study was standardized and based on questionnaires used in previous military studies,[63] but updated to include more DSs currently on the market and accessible to military personnel. The demographic characteristics and lifestyle factors examined in this study were similar to those of other civilian and military investigations, allowing for reasonable comparisons across studies. Although SMs reported the frequency of DS use, they did not report amounts (ie, doses) of DSs, so these could not be related to AEs. To adequately analyze the extensive data collected in this study a large number of statistical tests examining relationships between AEs and the demographic, lifestyle, and military factors were conducted. The more effects investigated, the greater the chance of making a Type 1 error where the null hypothesis will be incorrectly accepted. All data were self-reported and had the usual weaknesses associated with this method, including recall bias, social desirability, errors in self-observation, and inadequate recall.[64,65] Self-reported AEs could have misinterpreted in the case that, for example, a particular symptom caused by another event was associated with a DS taken in close proximity to the other event. Gender could only be reported as “male” or “female” on the questionnaire and there could have been participants who identify as nonbinary or have other gender identifications. Finally, it is important to note the perception that specific DSs are dangerous could bias individuals to report that a DS they are taking caused AEs when it actually did not. This may be considered a nocebo effect[66] because the symptoms are induced or associated with use of a DS by negative information on that DS, not consumption of the DS.

CONCLUSIONS

Clinicians should advise clients that DSs are not regulated by the FDA for their efficacy or safety and a number of these have been associated with AEs, especially those marketed for weight control, before/after workout, bodybuilding, and hormone enhancement. If clients choses to use DSs they need to be aware of the potential for AEs and to monitor themselves after consumption. Data in this study provide useful quantitative information that can assist in this regard: In this stratified random sample of more than 26,000 SMs from all military services, the prevalence of self-reported AEs was 18%. AE incidence was particularly high for combination products (20% of users) and purported prohormones (8% of users). Women, younger individuals, those with higher BMI, smokers, those with higher alcohol intake, and those consuming a greater number of DSs are at higher risk. Further research on the AEs of DSs might link specific DS to adverse medical events recorded in medical records rather than relying only on self-reported AEs. This could further improve the understanding of the association of DSs with their actual AEs.[67]

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AUTHOR INFORMATION

J. J. Knapik and H. R. Lieberman are a research physiologist, and E. K. Farina is a research nutritionist, Military Nutrition Division, US Army Research Institute of Environmental Medicine, Natick, MA. D. W. Trone is a research physiologist/epidemiologist, Naval Health Research Center, San Diego, CA. R. A. Steelman is an epidemiologist, US Army Public Health Center, Aberdeen Proving Ground, MD.

Address correspondence to: Joseph J. Knapik, ScD, Military Nutrition Division, US Army Research Institute of Environmental Medicine, 10 General Greene Ave, Natick, MA 01760. E-mail: joseph.j.knapik.civ@mail.mil

STATEMENT OF POTENTIAL CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

J. J. Knapik designed the research, analyzed data, wrote the paper, and had responsibility for final content. D. W. Trone designed the research, conducted research, provided essential materials, and had responsibility for final content. R. A. Steelman analyzed data and had responsibility for final content. E. K. Farina designed the research and had responsibility for final content. H. R. Lieberman conceptualized the study, designed the research plan, and had responsibility for final content. All authors read and approved the final manuscript.