SPECIAL ARTICLE

Emergency Department Visits for Adverse Events Related to Dietary Supplements

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ABSTRACT

BACKGROUND

Dietary supplements, such as herbal or complementary nutritional products and micronutrients (vitamins and minerals), are commonly used in the United States, yet national data on adverse effects are limited.

METHODS

We used nationally representative surveillance data from 63 emergency departments obtained from 2004 through 2013 to describe visits to U.S. emergency departments because of adverse events related to dietary supplements.

RESULTS

On the basis of 3667 cases, we estimated that 23,005 (95% confidence interval [CI], 18,611 to 27,398) emergency department visits per year were attributed to adverse events related to dietary supplements. These visits resulted in an estimated 2154 hospitalizations (95% CI, 1342 to 2967) annually. Such visits frequently involved young adults between the ages of 20 and 34 years (28.0% of visits; 95% CI, 25.1 to 30.8) and unsupervised children (21.2% of visits; 95% CI, 18.4 to 24.0). After the exclusion of unsupervised ingestion of dietary supplements by children, 65.9% (95% CI, 63.2 to 68.5) of emergency department visits for single-supplement–related adverse events involved herbal or complementary nutritional products; 31.8% (95% CI, 29.2 to 34.3) involved micronutrients. Herbal or complementary nutritional products for weight loss (25.5%; 95% CI, 23.1 to 27.9) and increased energy (10.0%; 95% CI, 8.0 to 11.9) were commonly implicated. Weight-loss or energy products caused 71.8% (95% CI, 67.6 to 76.1) of supplement-related adverse events involving palpitations, chest pain, or tachycardia, and 58.0% (95% CI, 52.2 to 63.7) involved persons 20 to 34 years of age. Among adults 65 years of age or older, choking or pill-induced dysphagia or globus caused 37.6% (95% CI, 29.1 to 46.2) of all emergency department visits for supplement-related adverse events; micronutrients were implicated in 83.1% (95% CI, 73.3 to 92.9) of these visits.

CONCLUSIONS

An estimated 23,000 emergency department visits in the United States every year are attributed to adverse events related to dietary supplements. Such visits commonly involve cardiovascular manifestations from weight-loss or energy products among young adults and swallowing problems, often associated with micronutrients, among older adults. (Funded by the Department of Health and Human Services.)

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Herbals (botanical products), complementary nutritionals (e.g., amino acids), and micronutrients (vitamins and minerals) are all considered to be dietary supplements by the Dietary Supplement Health and Education Act of 1994.[1] Although supplements cannot be marketed for the treatment or prevention of disease, they are often taken to address symptoms or illnesses, as well as to maintain or improve overall health.[2] The estimated number of supplement products increased from 4000 in 1994[3] to more than 55,000 in 2012 (the most recent year for which data are publicly available),[4] and approximately half of all adults in the United States report having used at least one dietary supplement in the past month.[5] In 2007, out-of-pocket expenditures for herbal or complementary nutritional products reached $14.8 billion, one third of the out-of-pocket expenditures for prescription drugs.[6]

The Food and Drug Administration (FDA) is tasked with the oversight of dietary supplements; if a dietary supplement is found to be unsafe, the FDA can have the manufacturer remove the product from the market. However, the regulatory framework differs from that for prescription or over-the-counter pharmaceuticals. Manufacturers of dietary supplements containing ingredients that were introduced after October 15, 1994, are required to notify the FDA before marketing and to provide a rationale for the safety of the ingredients, such as historical use. However, neither safety testing nor FDA approval is required before the marketing of dietary supplements.[7]

Postmarketing reporting of adverse events by dietary-supplement manufacturers is required only for serious[8] adverse events (e.g., those resulting in hospitalization, significant disability, or death), and voluntary reporting may substantially underestimate the adverse events associated with dietary supplements.[9,10] Postmarketing regulatory actions to remove adulterated supplement products from the market have received public attention. From 2004 through 2012, more than 200 recalls were issued for dietary supplements containing unapproved regulated substances or impurities,[11] and calls for changes in oversight have followed.[4,12-18]

The safety of dietary supplements that are not known to be adulterated remains poorly described,[19] however. Data are lacking to quantify the frequency of adverse events associated with dietary supplements in the United States.[4,20-24] We used nationally representative surveillance data to estimate the number of emergency department visits for adverse events related to dietary supplements and to identify the associated characteristics of the patients, products, and types of adverse events.

Methods

Data Collection

We estimated the number of emergency department visits for adverse events associated with dietary supplements in the United States using 10 years of data (from January 1, 2004, through December 31, 2013) from the 63 hospitals participating in the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project conducted by the Centers for Disease Control and Prevention (CDC), the FDA, and the Consumer Product Safety Commission. These hospitals make up a nationally representative probability sample drawn from all hospitals with at least six beds and 24-hour emergency departments (excluding psychiatric and penal institutions) in the United States and its territories, with four strata based on hospital size and a fifth stratum for pediatric hospitals.

Trained abstractors at each hospital reviewed the clinical records of every emergency department visit to identify physician-diagnosed adverse events and reported up to 2 implicated products and 10 concomitant products, as described previously.[25] Abstractors also recorded narrative descriptions of the event, including preceding circumstances, physician diagnoses, testing, treatments administered in the emergency department or by emergency medical services, and patient outcome. Narrative data were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 9.1. Since data collection is considered to be a public health surveillance activity, no approval from institutional ethics committees or review boards was required.[26]

Study Definitions

Cases were defined as emergency department visits for problems that the treating clinician explicitly attributed to the use of dietary supplements. This analysis included orally administered

herbal or complementary nutritional products (including botanicals, microbial additives, and amino acids) and micronutrients (vitamins and minerals) but excluded products that are typically considered to be foods or drinks (e.g., energy drinks, herbal tea beverages). Additional products that are often used by consumers for complementary health but do not fall under the regulatory definition of dietary supplements (e.g., topically administered herbal or homeopathic products) were also included in the analysis. Herbal or complementary nutritional products were categorized according to common reasons for use. (For detailed definitions and specific products, see Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

Adverse events were categorized as adverse reactions, allergic reactions, excess doses, unsupervised ingestion by children, or other events (e.g., choking). Cases involving death on the way to the emergency department or after arrival were excluded because death registration practices vary among participating hospitals, and details about event circumstances are often lacking. Visits involving intentional self-harm, drug abuse, therapeutic failures, nonadherence, or withdrawal were also excluded. The categorization of symptoms was based on MedDRA-coded narratives.

STATISTICAL ANALYSIS

The Consumer Product Safety Commission weighted cases of adverse events on the basis of the inverse probability of selection after adjustment for nonresponse and hospital nonparticipation and accounting for changes in the number of U.S. emergency department visits each year. We calculated national estimates as the sum of the number of cases multiplied by their respective weights and the corresponding 95% confidence intervals, using the SURVEYMEANS procedure in SAS software, version 9.3 (SAS Institute). Cumulative estimates and corresponding confidence intervals were divided by 10 to calculate average annual estimates and confidence intervals. We used the SURVEYFREQ procedure with the Rao–Scott modified chi-square test to assess differences in weighted proportions. We used SURVEYLOGISTIC and SURVEYREG procedures to assess linear trends in biennial estimates of emergency department visits. Biennial estimates were used to allow trend analyses to be conducted for categories of supplements associated with a small number of cases. We used intercensal estimates from the Census Bureau to calculate population rates. All analyses accounted for weighting and complex sample design. We considered that cumulative estimates of less than 1200, estimates that are based on fewer than 20 cases, or estimates with with coefficients of variation of more than 30% are statistically unreliable and are thus noted. Analyses of implicated products and symptoms were limited to cases in which a single dietary supplement product was implicated; unsupervised ingestions by children were analyzed separately.

RESULTS

SUPPLEMENT-RELATED EMERGENCY DEPARTMENT VISITS

On the basis of 3667 cases identified from 2004 through 2013, we calculated an average of 23,005 (95% confidence interval [CI], 18,611 to 27,398) emergency department visits for adverse events associated with dietary supplements annually and further estimated that these visits would result in an average of 2154 (95% CI, 1342 to 2967) hospitalizations annually (Table 1). In 88.3% of emergency department visits, clinicians attributed adverse events to only one supplement (as compared with multiple supplements). More than half of emergency department visits for supplement-related adverse events involved female patients. The mean age of patients who were treated for supplement-related adverse events was 32 years; more than a quarter (28.0%) of emergency department visits that were attributed to supplement-related adverse events involved persons 20 to 34 years of age. Persons 65 years of age or older were more likely to be hospitalized than were younger persons, with rates of 16.0% and 8.4%, respectively (P=0.003) (Table S3 in the Supplementary Appendix). One fifth of emergency department visits for supplement-related adverse events involved unsupervised ingestion by children.

PRODUCTS

Most emergency department visits for unsupervised ingestion of supplements by children involved a micronutrient product (61.9%; 95% CI, 56.5 to 67.3). The specific product categories that were most commonly implicated were multi-

Table 1. Number of Cases and National Estimates of Emergency Department Visits per Year for Adverse Events Associated with Dietary Supplements (2004–2013).*

Characteristic	No. of Cases	Emergency Department Visits per Year	
		estimated no.	*estimated % (95% CI)*
All patients	3667	23,005	
Age (yr)			
≤4	988	4,965	21.6 (18.9–24.3)
5–10	126	697	3.0 (2.3–3.7)
11–19	308	1,866	8.1 (6.7–9.6)
20–34	930	6,433	28.0 (25.1–30.8)
35–49	558	3,505	15.2 (13.6–16.8)
50–64	399	2,682	11.7 (9.8–13.5)
≥65	358	2,857	12.4 (10.1–14.7)
Sex			
Female	2121	13,402	58.3 (56.4–60.1)
Male	1546	9,602	41.7 (39.9–43.6)
Race†			
Black	577	2,547	11.1 (6.6–15.6)
White	1586	11,710	50.9 (40.6–61.2)
Other	552	3,166	13.8 (7.5–20.1)
Unknown	952	5,581	24.3 (15.2–33.3)
Number of implicated products			
1 Supplement implicated	3203	20,303	88.3 (86.3–90.2)
>1 Supplement implicated	97	536	2.3 (1.5–3.1)
Supplement and non-supplement implicated	367	2,165	9.4 (7.6–11.2)
Mechanism of adverse event‡			
Adverse reaction	1152	7,663	33.3 (29.9–36.7)
Allergic reaction	796	5,434	23.6 (21.1–26.2)
Unsupervised ingestion by child	946	4,871	21.2 (18.4 –24.0)
Excess dose	375	2,330	10.1 (8.8–11.4)
Other	398	2,707	11.8 (9.9–13.7)
Patient outcome‡			
Discharged	3267	20,850	90.6 (88.0–93.3)
Hospitalized	400	2,154	9.4 (6.7–12.0)

* Cases are identified in 63 hospitals in the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS–CADES) project. Included is a stratified probability sample of U.S. hospitals with 24-hour emergency rooms and at least six beds, which allows each case to be weighted on the basis of the number of similar cases it represents nationally. National estimates and confidence intervals were calculated as the sum of the number of cases multiplied by their respective weights. Additional information on sample design, data collection, and statistical properties is provided in the Supplementary Appendix.
† Race was not uniformly documented in all hospitals.
‡ Definitions are provided in Table S1 in the Supplementary Appendix.

vitamins (33.6%; 95% CI, 29.0 to 38.3), iron (11.8%; 95% CI, 8.6 to 15.0), supplements for weight loss (10.4%; 95% CI, 7.8 to 13.1), and supplements for sleep, sedation, or anxiolysis (8.8%; 95% CI, 6.0 to 11.5).

After the exclusion of unsupervised ingestion by children, 65.9% of emergency department visits for supplement-related adverse events involved a single herbal or complementary nutritional product; 31.8% involved a single micronutrient product (Table 2). After the exclusion of unsupervised ingestion by children, a weight-loss product was implicated in 25.5% of emergency department visits and an energy product in 10.0% of such visits.

Table 2. National Estimates of Emergency Department Visits for Adverse Events Associated with Dietary Supplements, According to Product Category (2004–2013).*

Product Category	Emergency Department Visits *estimated % (95% CI)*
Herbal or complementary nutritional product	65.9 (63.2–68.5)
Weight loss	25.5 (23.1–27.9)
Energy	10.0 (8.0–11.9)
Sexual enhancement	3.4 (2.4–4.3)
Cardiovascular health	3.1 (2.3–3.9)
Sleep, sedation, or anxiolysis	2.9 (2.1–3.6)
Laxative	2.5 (1.8–3.3)
Bodybuilding	2.2 (1.1–3.2)
Immunity or infection	2.2 (1.5–2.9)
Pain or arthritis relief	1.7 (1.2–2.3)
Detoxification or cleansing	1.4 (0.7–2.0)
Skin or hair health	1.0 (0.6–1.4)
Microbial additive	0.8 (0.4–1.3)†
Other specified	4.8 (3.7–5.9)
Unspecified	4.4 (3.3–5.4)
Micronutrient	31.8 (29.2–34.3)
Multivitamin or unspecified vitamin	16.8 (15.1–18.5)
Iron	4.7 (3.4–6.1)
Calcium	3.4 (2.5–4.3)
Potassium	2.0 (1.2–2.7)
Other single-ingredient vitamin or mineral	4.9 (3.6–6.2)
>1 Supplement product‡	2.4 (1.4 –3.3)

* Cases of unsupervised ingestion of dietary supplements by children are not listed here. Definitions and specific products are provided in Tables S1 and S2 in the Supplementary Appendix

† The national estimate in this category may be statistically unreliable, since it is based on fewer than 20 cases.

‡ Of 71 cases in which two supplement products were implicated, 45 implicated two herbal or complementary nutritional products, 6 implicated two micronutrient products, and 20 implicated both a micronutrient and an herbal or complementary nutritional product.

According to Sex of Patients

Weight-loss products were implicated in an estimated 3399 (95% CI, 2618 to 4180) emergency department visits per year by female patients, almost three times the number of emergency department visits by male patients associated with these products (1223; 95% CI, 858 to 1588) (Fig. 1). Of the total number of emergency department visits for supplement-related adverse events, weight-loss products were implicated in 30.4% (95% CI, 27.4 to 33.4) of such visits among female patients, as compared with 17.6% (95% CI, 14.3 to 20.9) among male patients. Sexual-enhancement products or bodybuilding products were implicated in 14.1% (95% CI, 10.5 to 17.7) of emergency department visits for supplement-related adverse events among male patients; there were too few cases among female patients to calculate a reliable estimate.

According to Age of Patients

After the exclusion of unsupervised ingestion by children, micronutrients were implicated in two thirds of emergency department visits for supplement-related adverse events among children 4 years of age or younger (67.3%) and adults 65 years of age or older (62.7%) (Table S4 in the Supplementary Appendix). In contrast, herbal or complementary nutritional products were most commonly implicated among the other age groups.

Weight-loss products or energy products were implicated in more than half the emergency department visits for supplement-related adverse events among patients 5 to 19 years of age (51.2%; 95% CI, 44.2 to 58.3) and those 20 to 34 years of age (56.4%; 95% CI, 51.8 to 61.1) (Fig. 2). Weight-loss products were implicated in 2661 (95% CI, 1995 to 3326) emergency department visits per year for supplement-related adverse events among patients 20 to 34 years of age, a number similar to that for visits associated with all other products combined among patients in each of the older age groups (Table S5 in Supplementary Appendix). Among adults 65

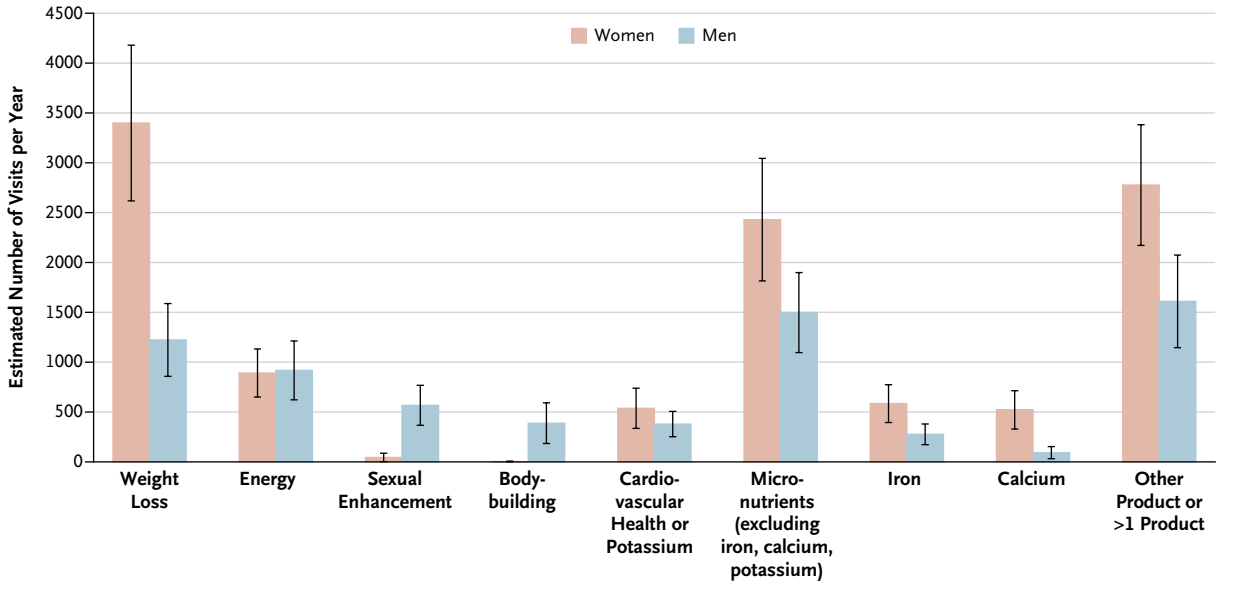

Figure 1. National Estimates of Emergency Department Visits for Adverse Events Associated with Dietary Supplements, According to Sex and Product Category (2004–2013).

Shown are the estimated number of emergency department visits per year, after the exclusion of unsupervised ingestion of dietary supplements by children, during a 10-year period. National estimates are based on fewer than 20 cases or have a coefficient of variation of more than 30% and may be statistically unreliable for the following combinations of product category and sex of the patient: sexual-enhancement products among women, bodybuilding products among women, and calcium among men.

years of age or older, three specific micronutrients (iron, calcium, and potassium) were implicated in almost one third (29.9%; 95% CI, 24.9 to 35.0) of emergency department visits for supplement-related adverse events.

SYMPTOMS

Cardiac symptoms (palpitations, chest pain, or tachycardia) were the most common symptoms associated with weight-loss products (in 42.9% of patients) and energy products (in 46.0% of patients) (Table 3). Weight-loss or energy products were implicated in 71.8% (95% CI, 67.6 to 76.1) of all emergency department visits for supplement-related adverse events involving palpitations, chest pain, or tachycardia. Most of the visits for cardiac symptoms (58.0%; 95% CI, 52.2 to 63.7) involved persons 20 to 34 years of age. Cardiac symptoms were also commonly documented in emergency department visits attributed to bodybuilding products (49.8%; 95% CI, 34.5 to 65.0) and sexual-enhancement products (37.3%; 95% CI, 25.3 to 49.3). Most patients with palpitations, chest pain, or tachycardia associated with supplement-related adverse events were discharged from the emergency department (89.9%; 95% CI, 87.2 to 92.6).

The most common adverse effects from most micronutrients (excluding iron, calcium, and potassium) were mild-to-moderate allergic reactions (40.6%) and swallowing problems (combination of choking and pill-induced dysphagia or globus, 41.0%; 95% CI, 32.4 to 49.7). Swallowing problems caused most emergency department visits involving calcium products (54.1%; 95% CI, 40.9 to 67.2), whereas abdominal symptoms (e.g., nausea, vomiting, and abdominal pain) were frequently associated with iron or potassium products.

Emergency department visits for supplement-induced swallowing problems were not common among patients 6 to 64 years of age (9.4%; 95% CI, 7.3 to 11.4) but were more common among those 65 years of age or older (37.6%; 95% CI, 29.1 to 46.2). Among older adults, 83.1% (95% CI, 73.3 to 92.9) of emergency department visits for supplement-induced swallowing problems involved micronutrients.

TRENDS OVER TIME

The estimated number of emergency department visits for supplement-related adverse events was 20,517 (95% CI, 15,187 to 25,847) annually in 2004–2005 and 26,779 (95% CI, 21,703 to 31,854) annually in 2012–2013. However, after accounting for population increases, the incidence of emergency department visits for supplement-related adverse events did not significantly change during this period (P=0.09). There were no significant changes in the estimated numbers of emergency department visits for supplement-related adverse events associated with herbal or complementary nutritional products, micronutrients, weight-loss products, or energy products or for unsupervised ingestion of dietary supplements by children. However, emergency department visits for adverse events associated with micronutrients (excluding iron, calcium, and potassium) increased from 3212 (95% CI, 1930 to 4493) annually in 2004–2005 to 4578 (95% CI, 3397 to 5759) annually in 2012–2013 (P=0.03 after accounting for population increases).

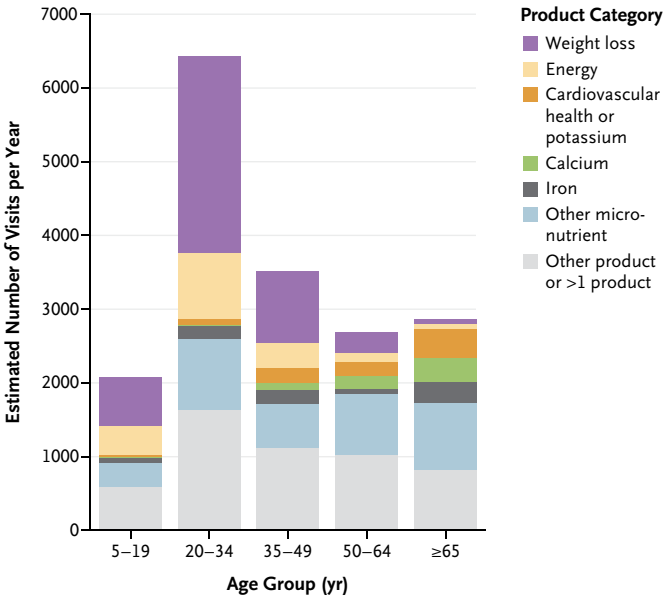

Figure 2. National Estimates of Emergency Department Visits for Adverse Events Associated with Dietary Supplements, According to Age Group and Product Category (2004–2013).

National estimates are based on fewer than 20 cases or have a coefficient of variation of more than 30% and may be statistically unreliable for the following combinations of age group and product category: weight loss (persons ≥65 years of age), energy (persons 50 to 64 years and ≥65 years of age), cardiovascular health or potassium (persons 5 to 19 years and 20 to 34 years of age), calcium (persons 5 to 19 years, 20 to 34 years, and 35 to 49 years of age), and iron (persons 5 to 19 years and 50 to 64 years of age).

DISCUSSION

On the basis of reports from a nationally representative sample of emergency departments from 2004 through 2013, we estimated that dietary supplements were implicated in an average of 23,000 emergency department visits and 2000 hospitalizations annually. Although the numbers of emergency department visits and hospitalizations were less than 5% of the numbers that have been reported for pharmaceutical products previously,[27] dietary supplements are regulated and marketed under the presumption of safety.

Although the incidence of emergency department visits for adverse drug events is reported to be low among young adults,[27] more than one quarter (28%) of emergency department visits for supplement-related adverse events in our study involved young adults between the ages of 20 and 34 years. Weight-loss or energy products caused more than half these visits, commonly for cardiac symptoms (palpitations, chest pain, or tachycardia). Notably, cardiac symptoms were documented more frequently in emergency department visits for adverse events associated with weight loss (43%) and energy products (46%) than for prescription stimulants. In a previous study[28] that used the same data source as the one used in our study, cardiac symptoms were documented in 23% of emergency department visits that were associated with prescription stimulants, which have label warnings for sympathomimetic adverse effects. Unlike over-the-counter or prescription medications, there are no requirements to identify adverse effects on dietary-supplement packaging. Clinicians could be encouraged to educate patients about potential cardiac effects from these products. However, since dietary-supplement histories are infrequently obtained,[29-32] particularly among young adults,[31] other opportunities for informing users of these potential adverse effects may be needed.

Unsupervised ingestions by children caused more than one fifth (21%) of all estimated emergency department visits for supplement-related adverse events, with almost two thirds involving micronutrients. Child-resistant packaging is not required for dietary supplements other than those containing iron,[33] and despite such pack-

Table 3. National Estimates of Symptoms Documented during Emergency Department Visits for Adverse Events Associated with Dietary Supplements from Selected Product Categories (2004–2013).*

Symptom	Emergency Department Visits *estimated % (95% CI)*
Supplements for weight loss	
Palpitations, chest pain, or tachycardia	42.9 (38.4–47.4)
Headache, dizziness, presyncope, or other acute sensory or motor impairment	32.1 (26.2–38.0)
Nausea, vomiting, or abdominal pain	18.6 (13.6–23.7)
Mild or moderate allergic reaction	14.3 (9.5–19.2)
Anxiety	12.9 (10.2–15.5)
Severe allergic reaction	4.2 (2.3–6.2)
Seizure, syncope, or loss of consciousness	4.0 (2.1–5.8)
Supplements for energy	
Palpitations, chest pain, or tachycardia	46.0 (39.1–52.9)
Headache, dizziness, presyncope, or other acute sensory or motor impairment	34.3 (25.7–43.0)
Nausea, vomiting, or abdominal pain	23.0 (15.9–30.1)
Anxiety	17.5 (11.4–23.7)
Micronutrients†	
Mild or moderate allergic reaction	40.6 (34.2–47.1)
Pill-induced dysphagia or globus	23.6 (17.1–30.0)
Airway obstruction from choking	19.4 (10.7–28.0)
Headache, dizziness, presyncope, or other acute sensory or motor impairment	7.0 (3.8–10.2)
Nausea, vomiting, or abdominal pain	6.5 (3.2–9.7)
Severe allergic reaction	6.1 (3.7–8.6)
Palpitations, chest pain, or tachycardia	3.8 (2.2–5.4)

* Cases of unsupervised ingestion of dietary supplements by children are not listed here. Symptoms are not mutually exclusive, so totals may be greater than 100%.
† Iron, calcium, and potassium are excluded from the micronutrient category.

aging, iron supplements were the second most commonly implicated type of supplement in unsupervised ingestion by children. Innovative safety packaging and targeted education on safe storage are potential interventions to reduce unsupervised ingestion of supplements by children.[34]

Among older adults, swallowing problems caused nearly 40% of emergency department visits for supplement-related adverse events, with micronutrients implicated in more than 80% of these visits. The FDA recommends limiting the size of pharmaceutical tablets to 22 mm and requires the reporting of tablet size and shape on abbreviated new-drug applications.[35] However, there are no size recommendations or similar reporting requirements for dietary supplements. Large amounts or multiple types of micronutrients are often packaged in a single large pill, and many micronutrient products approaching or exceeding 22 mm are commercially available.[36] Considerations for reducing the number of emergency department visits for swallowing problems include decreasing the size of supplement pills or using other delivery vehicles (e.g., liquids, gels, or powders), particularly for micronutrients for older adults, along with educating patients on methods for avoiding swallowing problems.

Limitations of our analysis should be noted. The number of emergency department visits attributed to supplement-related adverse events that we identified is probably an underestimation, since supplement use is underreported by patients, and physicians may not identify adverse events associated with supplements as often as they do those associated with pharmaceuticals.[29-31,37] Physicians also may have more limited knowledge of interactions between prescription drugs and dietary supplements than they do interactions between prescription drugs. In addition, we did not collect data on emergency department visits associated with products that are generally considered to be foods or drinks by consumers but that may be considered to be dietary supplements under the Dietary Supplement Health and Education Act (e.g., energy drinks). However, it is also possible that emergency department physicians may incorrectly attribute certain symptoms to supplements, which could lead to overestimation.

The relatively wide confidence intervals around the reported national estimates indicate the precision limitations of using a relatively small, albeit representative, sample of hospitals. Sample size and design also prevent identification of differences among metropolitan areas, states, or regions. Nonetheless, population-based active surveillance can quantify adverse events better than voluntary reporting.[10]

A limited regulatory framework makes it challenging to accurately monitor the safety of supplements.[18] It was not possible to calculate rates of emergency department visits for adverse events associated with supplements according to specific ingredient, product, or type, because data quantifying supplement use are extremely

limited. Estimates of overall supplement use are available from national surveys, but studies have used varying categorizations, and most lack product-specific data.[5,38] Identifying specific ingredients is also challenging because dietary supplements often contain multiple ingredients, and similarly named products can have different ingredients. For example, a product called Pro Clinical Hydroxycut Lose Weight lists 10 active ingredients, none of which are the three listed active ingredients in Hydroxycut Appetite Control.[39]

We categorized supplements on the basis of common reasons for use. In some cases, products were identified only by intended use (e.g., weight-lifting supplement). In other cases, specific products or ingredients were named, but because some products and ingredients are marketed for multiple uses (e.g., to improve energy and sexual performance), patients' reasons for use might have differed from assigned categories.

In conclusion, we estimate that more than 23,000 emergency department visits annually in the United States from 2004 through 2013 were for adverse events associated with dietary supplements. Such visits commonly involved cardiovascular adverse effects from weight-loss or energy herbal products among young adults, unsupervised ingestion of micronutrients by children, and swallowing problems associated with micronutrients among older adults. These findings can help target interventions to reduce the risk of adverse events associated with the use of dietary supplements.

The findings and conclusions in this study are those of the authors and do not necessarily represent the official position of the CDC or the FDA.

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REFERENCES

1. Dietary Supplement Health and Education Act of 1994. Public Law 103-417, 108 Stat 4325.
2. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. JAMA Intern Med 2013;173:355-61.
3. Report of the Commission on Dietary Supplement Labels. Washington, DC: Department of Health and Human Services, Office of Disease Prevention and Health Promotion, 1997 (http://web.health.gov/dietsupp/final.pdf).
4. Dietary supplements: FDA may have opportunities to expand its use of reported health problems to oversee products (GAO-13-244). Washington, DC: Government Accountability Office. March 18, 2013 (http://www.gao.gov/assets/660/653113.pdf).
5. Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003-2006. J Nutr 2011;141:261-6.
6. Nahin RL, Barnes PM, Stussman BJ, Bloom B. Costs of complementary and alternative medicine (CAM) and frequency of visits to CAM practitioners: United States, 2007. Natl Health Stat Report 2009:1-14.
7. Department of Health and Human Services, Food and Drug Administration. New dietary ingredients in dietary supplements — background for industry. March 3, 2014 (http://www.fda.gov/Food/DietarySupplements/NewDietaryIngredientsNotificationProcess/ucm109764.htm).
8. Dietary Supplement and Nonprescription Drug Consumer Protection Act. Public Law 109-462, 120 Stat 4500.
9. Adverse event reporting for dietary supplements: an inadequate safety valve (OEI-01-00-00180). Washington, DC: Department of Health and Human Services, Office of the Inspector General. April 2001 (http://oig.hhs.gov/oei/reports/oei-01-00-00180.pdf).
10. The Sentinel Initiative — national strategy for monitoring medical product safety. Washington, DC: Department of Health and Human Services, Food and Drug Administration. May 22, 2008 (http://www.fda.gov/downloads/Safety/FDAsSentinelInitiative/UCM124701.pdf).
11. Harel Z, Harel S, Wald R, Mamdani M, Bell CM. The frequency and characteristics of dietary supplement recalls in the United States. JAMA Intern Med 2013;173:926-8.
12. Dietary Supplement Labeling Act of 2013, S. 1425, 113th Cong. (2013).
13. Consumers Union. Consumers union endorses dietary supplement labeling act. August 1, 2013 (http://consumersunion.org/news/consumers-union-endorses-dietary-supplement-labeling-act).
14. Dietary Supplement Safety Act of 2010, S. 3002, 111th Cong. (2010).
15. Denham BE. Dietary supplements — regulatory issues and implications for public health. JAMA 2011;306:428-9.
16. Cohen PA, Maller G, DeSouza R, Neal-Kababick J. Presence of banned drugs in dietary supplements following FDA recalls. JAMA 2014;312:1691-3.
17. Cohen PA. Hazards of hindsight — monitoring the safety of nutritional supplements. N Engl J Med 2014;370:1277-80.
18. Starr RR. Too little, too late: ineffective regulation of dietary supplements in the United States. Am J Public Health 2015;105:478-85.
19. Gardiner P, Sarma DN, Low Dog T, et al. The state of dietary supplement adverse event reporting in the United States. Pharmacoepidemiol Drug Saf 2008;17:962-70.
20. Timbo BB, Ross MP, McCarthy PV, Lin CT. Dietary supplements in a national survey: prevalence of use and reports of adverse events. J Am Diet Assoc 2006;106:1966-74.
21. Department of Health and Human Services, Food and Drug Administration. 2008 Health and Diet Survey: topline frequency report (http://www.fda.gov/Food/FoodScienceResearch/ConsumerBehaviorResearch/ucm193895.htm).
22. Dennehy CE, Tsourounis C, Horn AJ. Dietary supplement-related adverse events reported to the California Poison Control System. Am J Health Syst Pharm 2005;62:1476-82.
23. Haller C, Kearney T, Bent S, Ko R, Benowitz N, Olson K. Dietary supplement adverse events: report of a one-year poison center surveillance project. J Med Toxicol 2008;4:84-92.
24. Gardiner P, Adams D, Filippelli AC, et al. A systematic review of the reporting of adverse events associated with medical herb use among children. Glob Adv Health Med 2013;2:46-55.
25. Jhung MA, Budnitz DS, Mendelsohn AB, Weidenbach KN, Nelson TD, Pollock DA. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveil-

lance Project (NEISS-CADES). Med Care 2007;45:Suppl 2:S96-S102.
26. Centers for Disease Control and Prevention. Distinguishing public health research and public health nonresearch. July 29, 2010 (http://www.cdc.gov/od/science/integrity/docs/cdc-policy-distinguishing-public-health-research-nonresearch.pdf).
27. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA 2006;296:1858-66.
28. Cohen AL, Jhung MA, Budnitz DS. Stimulant medications and attention deficit–hyperactivity disorder. N Engl J Med 2006;354:2294-5.
29. Hensrud DD, Engle DD, Scheitel SM. Underreporting the use of dietary supplements and nonprescription medications among patients undergoing a periodic health examination. Mayo Clin Proc 1999;74:443-7.
30. Ang-Lee MK, Moss J, Yuan CS. Herbal medicines and perioperative care. JAMA 2001;286:208-16.
31. Gardiner P, Kemper KJ, Legedza A, Phillips RS. Factors associated with herb and dietary supplement use by young adults in the United States. BMC Complement Altern Med 2007;7:39.
32. Gardiner P, Sadikova E, Filippelli AC, White LF, Jack BW. Medical reconciliation of dietary supplements: don't ask, don't tell. Patient Educ Couns 2015;98:512-7.
33. 16 C.F.R. § 1700.14 Subchapter E — Poison Prevention Packaging Act of 1970 Regulations, Part 1700 — Poison Prevention Packaging; 38 FR 21247, Aug. 7, 1973, as amended at 41 FR 22266, June 2, 1976; 48 FR 57480, December 30, 1983.
34. Budnitz DS, Salis S. Preventing medication overdoses in young children: an opportunity for harm elimination. Pediatrics 2011;127(6):e1597-e1599.
35. Size, shape, and other physical attributes of generic tablets and capsules: guidance for industry. Silver Spring, MD: Food and Drug Administration Center for Drug Evaluation and Research. June 18, 2015 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377938.pdf).
36. Puritan's Pride. Multivitamins (http://www.puritan.com/multivitamins-067?cm_re=LeftNav-_-Link-_-Multivitamins).
37. Kaye AD, Clarke RC, Sabar R, et al. Herbal medicines: current trends in anesthesiology practice — a hospital survey. J Clin Anesth 2000;12:468-71.
38. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. 2011–2012 National Health and Nutrition Examination Survey (NHANES): dietary supplements and prescription medication. May 1, 2012 (http://www.cdc.gov/nchs/data/nhanes/nhanes_11_12/dsq.pdf).
39. Iovate Health Sciences International. Hydroxycut weight loss products (http://www.hydroxycut.com/products).