Original Contribution

Use of a Prescribed Ephedrine/Caffeine Combination and the Risk of Serious Cardiovascular Events: A Registry-based Case-Crossover Study

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Ephedrine and herbal ephedra preparations have been shown to induce a small-to-moderate weight loss. Owing to reports on serious cardiovascular events, they were banned from the US market in 2004. There have been no large controlled studies on the possible association between prescribed ephedrine/caffeine and cardiovascular events in general. The authors linked data from four different sources within Statistics Denmark, using data on 257,364 users of prescribed ephedrine/caffeine for the period 1995–2002. The data were analyzed using a case-crossover technique with a composite endpoint: death outside of a hospital, myocardial infarction, or stroke. To account for effects of chronic exposure and effects in naïve users, the authors performed a secondary case-control study nested within the cohort of ephedrine/caffeine ever users. Among 2,316 case subjects, 282 (12.2%) were current users of ephedrine/caffeine. The case-crossover analysis yielded an odds ratio of 0.84 (95% confidence interval: 0.71, 1.00); after adjustment for trends in ephedrine/caffeine use, it was 0.95 (95% confidence interval: 0.79, 1.16). Subgroup analyses revealed no strata with significantly elevated risk. In the case-control substudy, there was no increased risk among naïve users or users with large cumulative doses. Prescribed ephedrine/caffeine was not associated with a substantially increased risk of adverse cardiovascular outcomes in this study.

Ephedra sinica; ephedrine; mortality; myocardial infarction; stroke

Abbreviations: CI, confidence interval; ICD, *International Classification of Diseases*; OR, odds ratio.

Ephedrine is a sympathomimetic compound with lipolytic and appetite-inhibiting properties (1). It is an alkaloid extract from ephedra shrubs growing in Asia, Europe, and America. The Asian species (*Ephedra sinica*) has the highest alkaloid content, and it has been used in traditional folk remedies (ma huang), particularly in China (2). In Western countries, ephedrine has been used to promote weight loss and to enhance athletic performance (1). During the 1990s, it was found that nearly one-third of young, obese women had used a weight-loss supplement containing ephedra (3). In 1999 alone, 12 million persons in the United States used 3 billion doses of ephedra alkaloids (3). The US Food and Drug Administration banned the sale of ephedrine in 2004 because of a considerable number of reports of adverse vascular complications (4).

The suspicion of cardiovascular toxicity of ephedrine was mainly based on spontaneous reporting (2, 3, 5). There were no large-scale controlled observational studies conducted to broadly assess the cardiovascular toxicity of ephedrine. Until 2002, a prescribed ephedrine preparation, Letigen (Nycomed International Management GmbH, Zurich, Switzerland), had a dominant position in the Danish market for weight-loss products. The existence of a national prescription database with comprehensive recording of all prescriptions filled in Denmark since 1995, with the possibility of linkage to a wide array of other health databases (6), offered us a unique opportunity to address the question of ephedrine's cardiovascular toxicity in a controlled observational study.

MATERIALS AND METHODS

Use of prescribed ephedrine in Denmark

Letigen was a pharmaceutical product containing 20 mg of synthetic ephedrine and 200 mg of caffeine, available

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only by prescription. Its recommended dose was 1–3 tablets per day, depending on the user's tolerance. It was approved for sale in Denmark in 1990. During the peak of its use in 1999, some 110,000 persons, corresponding to 2% of the Danish population, were treated (7). In 2002, the marketing license was suspended, after a number of reports had suggested a safety problem.

Data sources

We used data from Statistics Denmark, a governmental institution that collects and maintains electronic records for statistical and scientific purposes. Four comprehensive national data sources were used: the Danish National Registry of Patients, the Prescription Database of the Danish Medicines Agency, the Danish Register of Death, and the Danish Person Registry. All data sources were linked by use of a mutual identifier.

Since 1977, data on all individual hospital discharges have been stored in the Danish National Registry of Patients. Each record contains an identifier as well as selected medical data, including discharge diagnoses and operative procedures. Diagnoses were recorded according to the *International Classification of Diseases*, Eighth Revision (ICD-8), from 1977 through 1993 and have been recorded according to the *International Classification of Diseases*, Tenth Revision (ICD-10), since 1994. Virtually all inpatient medical care in Denmark during the study period (1995–2001) was furnished by the public health authorities; thus, this data resource allows true population-based studies, covering all 5.4 million inhabitants of Denmark (8).

The Prescription Database of the Danish Medicines Agency contains data on all prescriptions redeemed by Danish citizens since 1995, independently of whether or not the cost of the medication was reimbursed. Among the data included are a person identifier, the date of purchase, a prescriber code, the substance, the brand name, and the quantity dispensed. Dosing instructions and the indication for prescribing the medication are not recorded. Drugs are categorized according to the Anatomic-Therapeutic-Chemical classification (9).

The Danish Register of Death contains information on date of death, cause of death, and mode of death (natural cause, accident, suicide, or homicide) and a code indicating the location where the death occurred (in a hospital, at another health institution, at home, or elsewhere). The Danish Person Registry contains data on all migrations into and out of Denmark, which allowed us to keep track of all ephedrine/caffeine users.

The base population for this study was all persons who had filled prescriptions for ephedrine/caffeine during the period January 1, 1995–December 31, 2001. For this cohort of 298,848 persons, we extracted data on all prescriptions for cardiovascular, antithrombotic, antidiabetic, antirheumatic, antiasthmatic, and appetite-suppressant medications filled during the same period, and from the other registers, we obtained all available information on the subjects.

Analysis

Design. For our primary analysis, we used the case-crossover design. It is based on the case-base paradigm, but instead of the use of matched controls, the past experience of the case serves as the case's own reference. Thereby, confounders that are stable over time cancel each other out. This even extends to stable confounders that cannot be measured or are unknown (10–12). In the present context, use of ephedrine/caffeine could have been related to smoking and obesity (13). Case-crossover designs are particularly suitable when the exposure is intermittent, the effect on risk is immediate and transient, and the outcome is abrupt (10). The available reports suggested that the potential cardiovascular toxicity would indeed be immediate and transient and that the outcome would be abrupt (2, 3, 5).

Certain aspects of our research question were not amenable to a case-crossover study. Some spontaneous reports had suggested a particular risk in naïve, first-time users (3). Since subjects could not be naïve users both on their case date and on their control date, this would violate the conditions for a crossover study. We also wanted to study the effect of chronic exposure, for which the crossover type of study is inefficient (11). Finally, we wanted to explore a possible cumulative dose effect, for which the crossover design would not work (highest cumulative dose on the reference date would be impossible). To address these issues, we conducted a supplementary case-control study. To minimize potential confounding by indication, we nested the case-control study within a cohort of ever users of ephedrine/caffeine as described below.

Study cohort definition. Both the case-crossover study and the case-control study were nested within a cohort of ever users of ephedrine/caffeine. Persons entered the cohort and were eligible to become cases when all of the following events had occurred: 1) the start of the study period on July 1, 1996; 2) January 1 of the year of the subject's 18th birthday; 3) the filling of the first recorded ephedrine/caffeine prescription; and 4) residence in Denmark for at least 18 months. Thus, we required all subjects to have been observable for any medication dispensation for at least 18 months and to have filled at least one prescription for ephedrine/caffeine.

The subjects left the cohort at the first occurrence of one of the following: 1) any case-defining event; 2) death or emigration; 3) January 1 of the year of the subject's 70th birthday; 4) any diagnosis of malignancy, excluding non-melanoma skin cancer (ICD-10 codes C00–C97, excluding code C44; ICD-8 codes 140–207, excluding code 173); and 5) the end of study period on December 31, 2001.

We excluded persons who underwent one of the cohort-terminating events (e.g., a cancer diagnosis or emigration) before their potential cohort entry and persons who had more than one migration event.

Case definition. Since the literature on adverse effects of ephedrine is ambiguous about what particular cardiovascular effects to expect (2–5), we employed a broad, composite primary endpoint and performed secondary analyses on each subset of this endpoint.

Our primary endpoint was defined by the occurrence of any of the following:

- Death coded as due to natural causes, occurring outside of a hospital or nursing home.
- Myocardial infarction, defined by hospitalization with a discharge diagnosis of myocardial infarction (ICD-10

codes I21–I22). We also required that the hospital stay be at least 3 days in duration, unless the patient died within the first 3 days of admission. To account for hospital transfers for invasive procedures or other specialist treatment, serial admissions with no discharge interval between them were considered a single admission. Fatal myocardial infarction was defined as the patient's dying within 30 days after the index hospitalization.

- Stroke, defined by hospitalization with an ICD-10 discharge code of I61, I63, or I64, excluding codes I63.1 and I63.4 (cerebral embolism). Duration-of-stay and case-fatality criteria similar to those for the myocardial infarction cases were applied.

Exposure definition. We computed the frequency distributions of intervals between presentations of prescriptions for ephedrine/caffeine. On the basis of these analyses, we estimated the modal intake as slightly less than 2 tablets per day (14). Very few users had taken 4 or more tablets per day for extended periods of time. In our main analysis, we assigned a period of exposure for each prescription, starting on the day of prescription redemption and assuming a daily intake of 2 tablets, until all tablets were taken. Subjects were considered exposed on all days within a prescription's supply period and unexposed on all other days. As a sensitivity analysis, we repeated all analyses with an assumed daily intake of 1 or 3 tablets and with a fixed 90-day exposure period assigned to each prescription.

Our exploratory analyses confirmed the episodic nature of ephedrine/caffeine therapy. Using a waiting-time-distribution technique (14), we arrived at an average duration varying between 8.8 months and 13 months for the period 1995–2001. For other medications included as time-dependent covariates, we employed a fixed 90-day window to define exposure; that is, a person was considered exposed to aspirin if he or she had filled a prescription for aspirin within the past 90 days.

Case-crossover study. In the case-crossover design, a patient's exposure status at the time of disease is compared with the same patient's individual exposure at an earlier point in time. For each case subject, 10 control dates were assigned randomly within the period 9–15 months before the case date for the same individual. For cases that arose shortly after cohort entry, this entailed sampling control dates before cohort entry. We chose these control dates because of the seasonality in ephedrine/caffeine use. For example, there were approximately twice as many new users in January as in December and a small excess of use in the early summer months.

Time-dependent potential confounders were controlled by conditional logistic regression (10). We included use of low-dose aspirin, statins, antihypertensive agents, antidiabetic agents, and nonsteroidal antiinflammatory drugs as time-dependent covariates in all analyses. We also conducted analyses without inclusion of these covariates, but results are not presented, since they differed very little from those of the main analysis. We calculated odds ratios for our main endpoint, for each subset of endpoints, and for a number of prespecified patient subgroups as detailed in the tables.

Table 1. Characteristics of all users and of those experiencing a case-defining event[a] among 257,364 users of a fixed-dose caffeine/ephedrine product, Denmark, 1995–2001

	All Ephedrine/ Caffeine Users (*n* = 257,364)		Cases (*n* = 2,316)	
	No.	%	No.	%
Person-years of follow-up	1,023,297		5,534	
Men	51,974	20.2	1,019	44.0
Median age, years	36 (28–48)[b]		55 (47–61)	
Secondary endpoints				
Death outside hospital			531	22.9
Myocardial infarction			839	36.2
Fatal myocardial infarction			55	2.4
Stroke			946	40.8
Fatal stroke			58	2.5
Prior diagnosis of:				
Obesity	11,389	4.4	264	11.4
Diabetes	6,518	2.5	264	11.4
Hypertension	26,391	10.3	245	10.6
Chronic obstructive pulmonary disease	3,515	1.4	187	8.1
Ischemic heart disease	5,329	2.1	327	14.1
Cerebrovascular disease	1,414	0.5	146	6.3
Prior use of:				
Acetylsalicylic acid	6,884	2.7	348	15.0
Antihypertensive agents	57,521	22.4	1,178	50.9
Statins	5,587	2.2	195	8.4
Antidiabetic agents	6,935	2.7	283	12.2

[a] Death outside of a hospital, myocardial infarction, or stroke.
[b] Numbers in parentheses, interquartile range.

Adjustment for trends in exposure. There was a moderate decline in ephedrine/caffeine use during the last part of the study period, and the prevalence of ephedrine/caffeine use declined rapidly with age for persons aged 55 years or older (7). This would convey a spurious protective effect of ephedrine/caffeine; cases were less likely to use ephedrine/caffeine on their case date than on their control date, since they were approximately 1 year older and possibly had entered a period of lower ephedrine/caffeine use in general.

To adjust for this, Suissa (15) proposed the case-time-control design. A matched control group is extracted, and their exposure attributes on the index day and on a control date in the past are established in exactly the same ways as for the cases. Control subjects are then used as a reference group for the odds ratio derived from the case-crossover study (15). For each subject, we used 4 random controls selected as described below.

Case-control study. In the case-control substudy, we used the same cases and the same exposure definition as in the case-crossover study. For each case, we randomly selected 10 control subjects matched to the case with respect

Table 2. Main results from a case-crossover analysis of the association between use of prescribed ephedrine/caffeine and cardiovascular morbidity, Denmark, 1995–2001[a]

Endpoint	Cases			Case-Crossover Estimate[b]		Case-Time-Control Estimate[c]	
	Total No.	Exposed to Ephedrine/ Caffeine		AOR	95% CI	AOR	95% CI
		No.	%				
Main composite endpoint[d]	2,316	282	12.2	0.84	0.71, 1.00	0.95	0.79, 1.16
Secondary endpoints							
Death outside of a hospital	531	50	9.4	0.53	0.36, 0.79	0.54	0.35, 0.84
Myocardial infarction	839	109	13.0	0.94	0.71, 1.25	1.14	0.83, 1.56
Fatal myocardial infarction	55	6	10.9	0.53	0.16, 1.71	1.43	0.40, 5.14
Stroke	946	123	13.0	0.95	0.73, 1.23	1.07	0.80, 1.43
Fatal stroke	58	7	12.1	0.46	0.17, 1.27	0.92	0.29, 2.87

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

[a] The analysis was based on the assumption of an intake of 2 tablets per day starting from the day on which the prescription was filled. For each case subject, 10 random control days were sampled within the interval of 9–15 months prior to the index date.

[b] Adjusted for discordant use of aspirin, statins, antihypertensive agents, antidiabetic agents, and nonsteroidal antiinflammatory drugs by conditional logistic regression.

[c] Adjusted for discordant use of aspirin, statins, antihypertensive agents, antidiabetic agents, and nonsteroidal antiinflammatory drugs and for trend in ephedrine/caffeine prescriptions.

[d] Death outside of a hospital, myocardial infarction, or stroke.

to exact birth year and sex among the persons available in the cohort on the index date. Controls were assigned an index date identical to that of the case date of the corresponding case. Since we sampled controls from our study cohort, the reference category for comparison of current ephedrine/caffeine exposure was remote use of the medication.

In the case-control study, we placed a special focus on potential dose-response and duration-response effects. We used the number of tablets purchased within the last 90 days before the index date as a measure of current dose and the cumulative amount of ephedrine/caffeine ever recorded up to the index date as a measure of cumulative dose. For the duration-response effect, we categorized subjects according to the time of the first recorded prescription relative to the index date.

The following variables were included as potential confounders: 1) ever diagnosis of obesity (ICD-10 code E66; ICD-8 code 27799); 2) ever use of antidiabetic agents or a diagnosis of diabetes (ICD-10 codes E10–E14; ICD-8 code 250); 3) current use of low-dose acetylsalicylic acid; 4) ever diagnosis of chronic obstructive pulmonary disease (ICD-10 code J44; ICD-8 codes 490–491) or ever use of systemic beta-agonists or inhaled anticholinergic agents; 5) ever diagnosis of hypertension (ICD-10 code I10; ICD-8 code 40) or ever use of antihypertensive agents (i.e., thiazides, beta-blockers, calcium channel blockers, and medications acting on the renin-angiotensin system); 6) ever use of statins; 7) ever diagnosis of ischemic heart disease or myocardial infarction (ICD-10 codes I20–I25; ICD-8 codes 412–414); and 8) ever diagnosis of cerebral ischemia or stroke (ICD-10 codes I61, I63, and I64, excluding codes

I631 and 641; ICD-8 codes 431 and 433–435). Confounders were controlled by conditional logistic regression.

For all estimates, we report 95% confidence intervals.

The study was approved by Statistics Denmark's scientific board. Approval from an ethics committee was not required according to Danish law. Data were analyzed using Stata, version 8.0 (Stata Corporation, College Station, Texas).

RESULTS

Study cohort

Of the 298,848 persons registered as using ephedrine/ caffeine, 41,484 did not enter the study cohort, for the following reasons: 1) the subject was outside the allowed age range of 18–70 years throughout the study period ($n = 11,347$); 2) a cancer diagnosis or other cohort-terminating event preceded potential cohort entry ($n = 25,395$); and 3) more than one migration event was recorded ($n = 4,445$) or the subject immigrated too late to be observable for 18 months ($n = 297$). In all, 257,364 users of ephedrine/caffeine (51,974 men and 205,390 women) entered the cohort. They contributed 1,023,297 person-years of observation, during which 2,316 case-defining events occurred. Their clinical characteristics are detailed in Table 1.

Case-crossover study

Of the 2,316 cases, 531 were deaths that occurred outside of a hospital, 839 were myocardial infarctions, and 946 were strokes. The characteristics of the case subjects are listed in Table 1. Their median age was 55 years, and 1,019 (44%)

Table 3. Results from subgroup analysis in a case-crossover study of the association between use of prescribed ephedrine/caffeine and cardiovascular morbidity, Denmark, 1995–2001[a]

Subgroup	No. of Cases	No. of Exposed Cases	Case-Crossover Estimate[b]		Case-Time-Control Estimate[c]	
			AOR	95% CI	AOR	95% CI
Total	2,316	282	0.84	0.71, 1.00	0.95	0.79, 1.16
Sex						
Men	1,019	132	1.06	0.82, 1.37	1.28	0.96, 1.71
Women	1,297	150	0.70	0.56, 0.88	0.76	0.59, 0.99
Age group, years						
$\leq$39	199	27	1.04	0.60, 1.81	1.10	0.59, 2.03
40–59	1,182	152	0.95	0.75, 1.20	0.99	0.76, 1.29
$\geq$60	935	103	0.67	0.50, 0.89	0.90	0.65, 1.24
Prior diagnosis of diabetes or use of antidiabetic agents	355	45	0.84	0.53, 1.33	1.19	0.67, 2.09
Prior diagnosis of ischemic heart disease	327	27	0.55	0.33, 0.92	0.79	0.41, 1.51
Prior diagnosis of chronic obstructive pulmonary disease or use of inhaled anticholinergic agents	329	47	1.05	0.68, 1.61	1.29	0.75, 2.23
Prior diagnosis of cerebrovascular disease	146	30	2.49	1.38, 4.51	1.40	0.57, 3.42
Prior use of statins	195	15	0.40	0.20, 0.80	0.42	0.18, 0.93
Prior diagnosis of hypertension or use of antihypertensive agents	1,259	150	0.80	0.63, 1.01	1.07	0.81, 1.40
Prior diagnosis of obesity	264	32	1.09	0.65, 1.84	1.82	0.96, 3.45
No cardiovascular antecedents[d]	844	102	0.81	0.61, 1.08	0.84	0.62, 1.14

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

[a] The analysis was based on the assumption of an intake of 2 tablets per day starting from the day on which the prescription was filled. For each case subject, 10 random control days were sampled within the interval of 9–15 months prior to the index date. The main composite endpoint was employed for all analyses (see Table 2).

[b] Adjusted for discordant use of aspirin, statins, antihypertensive agents, antidiabetic agents, and nonsteroidal antiinflammatory drugs by conditional logistic regression.

[c] Adjusted for discordant use of aspirin, statins, antihypertensive agents, antidiabetic agents, and nonsteroidal antiinflammatory drugs and for trend in ephedrine/caffeine prescriptions.

[d] No prior cardiovascular diagnoses or use of cardiovascular, antidiabetic, antithrombotic, or antihypertensive medications.

were men. As expected, cardiovascular risk factors were more prevalent among cases than among users of ephedrine in general; 50.9% had a history of antihypertensive use, 15.0% of acetylsalicylic acid use, and 12.2% of antidiabetic use. Of the cases, 282 (12.2%) were current users of ephedrine/caffeine, the remaining being past users.

Among the 2,316 cases, 824 (36%) showed some degree of discordant exposure—that is, they were either exposed on the case date and unexposed on one or more of the reference dates or they were unexposed on the case date and exposed on at least one reference date. The odds ratio associating ephedrine/caffeine use with an adverse cardiovascular outcome, adjusted for discordant use of other cardiovascular medications and antidiabetic agents, was 0.84 (95% confidence interval (CI): 0.71, 1.00). Further adjustment for trend in ephedrine prescriptions yielded an odds ratio of 0.95 (95% CI: 0.79, 1.16). The odds ratios for sub-endpoints are shown in Table 2. For death occurring outside of a hospital, there was an inverse association with current ephedrine use (adjusted odds ratio (OR) = 0.54, 95% CI: 0.35, 0.84).

The explorative analyses revealed no subjects whose odds ratios were substantially elevated above the main group (Table 3). For women and for users of statins, an inverse association was observed (OR = 0.76 (95% CI: 0.59, 0.99) and OR = 0.42 (95% CI: 0.18, 0.93), respectively). The 95% confidence intervals for all other estimates spanned the null value.

The sensitivity analyses assuming a daily intake of 1 or 3 tablets or assigning a fixed 90-day window to each ephedrine prescription produced odds ratios of the same magnitude as those seen in the main analysis. The odds ratios for the main estimate were 1.20 (95% CI: 1.00, 1.43), 0.90 (95% CI: 0.73, 1.10), and 1.08 (95% CI: 0.90, 1.29), respectively.

Case-control study

In the case-control substudy, an odds ratio of 1.23 (95% CI: 0.67, 2.27) was found for the subgroup whose first ephedrine prescription was filled 0–10 days before the index

Table 4. Results from explorative dose-response and dose-duration analyses in a case-control study of the association between use of prescribed ephedrine/caffeine and cardiovascular morbidity, Denmark, 1995–2001[a]

Exposure Level	No. of Exposed Cases	No. of Unexposed Cases	No. of Exposed Controls	No. of Unexposed Controls	Crude OR	95% CI	Adjusted OR[b]	95% CI	Trend	
									OR	95% CI
No. of days since first prescription									0.89	0.82, 0.97
0–10	13	2,034	95	19,502	1.35	0.75, 2.44	1.23	0.67, 2.27		
11–19	12	2,034	90	19,502	1.35	0.73, 2.49	1.41	0.75, 2.66		
20–39	26	2,034	152	19,502	1.53	0.99, 2.36	1.32	0.83, 2.10		
40–79	18	2,034	175	19,502	0.95	0.56, 1.59	0.86	0.50, 1.47		
80–159	22	2,034	183	19,502	1.15	0.73, 1.81	1.11	0.70, 1.77		
≥160	191	2,034	2,233	19,502	0.83	0.71, 0.97	0.79	0.67, 0.93		
Cumulative dose within past 90 days, no. of tablets									0.95	0.81, 1.10
0–99	19	2,034	143	19,502	1.21	0.73, 1.98	1.12	0.67, 1.87		
100–199	126	2,034	1,322	19,502	0.91	0.75, 1.11	0.88	0.72, 1.07		
200–299	112	2,034	1,196	19,502	0.92	0.75, 1.13	0.87	0.71, 1.07		
300–399	16	2,034	173	19,502	0.91	0.54, 1.52	0.77	0.45, 1.32		
≥400	9	2,034	94	19,502	0.90	0.45, 1.79	0.84	0.41, 1.69		
Lifetime cumulative dose, no. of tablets									0.93	0.85, 1.01
0–99	8	2,034	60	19,502	1.30	0.62, 2.76	1.16	0.54, 2.52		
100–199	46	2,034	364	19,502	1.18	0.85, 1.63	1.08	0.77, 1.51		
200–399	57	2,034	559	19,502	0.98	0.74, 1.31	0.91	0.68, 1.22		
400–799	56	2,034	638	19,502	0.83	0.62, 1.10	0.80	0.60, 1.06		
800–1,599	65	2,034	671	19,502	0.96	0.74, 1.25	0.93	0.71, 1.22		
≥1,600	50	2,034	636	19,502	0.77	0.57, 1.03	0.74	0.55, 0.99		

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] The main composite endpoint was used in all analyses (see Table 2).

[b] Adjusted for a prior diagnosis of obesity, diabetes, hypertension, ischemic heart disease, chronic obstructive pulmonary disease, cerebral ischemia, or stroke and for ever use of antidiabetic agents, thiazides, beta-blockers, calcium channel blockers, medications acting on the renin-angiotensin system, inhaled anticholinergic agents, systemic beta-agonists, and statins. (See text for details.)

date (Table 4). The odds ratio decreased slightly with increasing duration since the first ephedrine/caffeine prescription (for each successive step, OR = 0.89, 95% CI: 0.82, 0.97). We found no indication of a trend with lifetime cumulative dose (per step, OR = 0.93, 95% CI: 0.85, 1.01) or cumulative dose within the past 90 days (per step, OR = 0.95, 95% CI: 0.81, 1.10).

In the case-control substudy, the adjusted odds ratios for the main composite endpoint, for death outside a hospital, for myocardial infarction, and for stroke were 0.88 (95% CI: 0.77, 1.01), 0.76 (95% CI: 0.54, 1.07), 0.95 (95% CI: 0.76, 1.18), and 0.92 (95% CI: 0.75, 1.13), respectively (data not shown).

DISCUSSION

Our main finding was that prescription of an ephedrine/caffeine product was not associated with adverse cardiovascular outcomes. This was found across a wide range of patient subgroups, different cardiovascular outcomes, different assumptions about exposure, and different utilization patterns.

The strength of our study is the comprehensive recording of clinical details for a very large population with virtually no loss to follow-up. One limitation of our study is that it concerned a pharmaceutical ephedrine preparation, produced under strict control. Findings may not be applicable to herbal products whose content of ephedra alkaloids varies substantially (16). In addition, herbal products may be used under less appropriate instruction or surveillance.

The evidence linking ephedrine to cardiovascular morbidity is based mainly on spontaneous reporting. However, with the very large number of users (3) and their possible adverse health behavior (13), coincidental cardiovascular events probably occur in large numbers.

There have been only a few controlled observational studies on ephedra alkaloids and cardiovascular outcomes. In the Hemorrhagic Stroke Project, an association was found between phenylpropanolamine and hemorrhagic stroke (17). Phenylpropanolamine is a minor metabolite of ephedrine which, in its synthetic form, is used as a cold remedy and

dieting aid. The association depended strongly on whether the substance was used for colds or for weight loss (OR = 1.2 vs. OR = 15.9), which may suggest some confounding by obesity. In a substudy exclusively evaluating exposure to genuine ephedra alkaloids, an overall null finding was reported (OR = 1.0), with a possible detrimental effect with large doses (OR = 3.6, 95% CI: 0.7, 18) (18). In a recent study from South Korea, Yoon et al. (19) reported an association between phenylpronalolamine and stroke, even when it was used against cold. In a meta-analysis of randomized studies of ephedra alkaloids, no serious cardiovascular events were observed among the subjects, and the authors were able to confidently exclude event rates above 1 per 1,000 treated persons (1).

A major prerequisite for the case-crossover design is that the unmeasured confounders are stable over time. Obviously, smoking behavior or body mass index may change over a year for an individual. However, stable tobacco abstinence or weight loss is an exception rather a rule (20, 21), and smokers continue to have a high cardiovascular risk for some time after having stopped smoking (22), as do persons who have lost weight (23). Thus, within the time frames of our study, the individual health effects of smoking and overweight were reasonably stable and were unlikely to have confounded our estimates materially.

For one endpoint, death occurring outside of a health institution, we observed odds ratios below unity. This should not be taken too literally as a protective effect. One possible explanation is that some of these subjects died at home from chronic nonmalignant diseases that had not resulted in secondary care contacts. These subjects were obviously very unlikely to have used ephedrine/caffeine shortly before their deaths. In addition, some subjects with impending cardiovascular events could have been warned by subtle symptoms and could have chosen to discontinue use of ephedrine for fear of its claimed toxicity. We performed a subanalysis in subjects with no prior cardiovascular diagnoses and no prior use of cardiovascular, antidiabetic, antithrombotic, or antihypertensive agents (Table 3). The estimate for this subgroup differed very little from the main estimate (OR = 0.81, 95% CI: 0.61, 1.08; after adjustment for trend, OR = 0.84, 95% CI: 0.62, 1.14). These "confounding-by-contraindication" effects are difficult to manage in observational studies, insofar as the warning symptoms are not always captured by available data sources, and we cannot rule out the possibility that the odds ratios for the main estimates may have been biased downward.

Another limitation is that in our main analysis, we assumed an immediate effect of ephedrine/caffeine. If an adverse effect of ephedrine/caffeine had delayed onset (e.g., if it were mediated through a hypertensive effect), we might not have captured it by our crossover analysis. However, there was nothing in our case-control analysis to suggest a delayed effect with continuous exposure.

Regarding the possibility of misclassification of case or exposure status, recent validations in our setting have shown positive predictive values on the order of 95% for both myocardial infarction and stroke diagnoses (24, 25). The prescription data in our data sources have a high level of accuracy (26). The main uncertainty regarding exposure was the exact timing of ephedrine intake relative to the filling of the prescriptions. Our sensitivity analyses showed the findings to be robust within reasonable assumptions about daily intake.

Our results have two major implications. First, we should not blindly trust the findings of spontaneous reporting schemes. Such systems are vulnerable to a "snowball" effect, whereby products that have acquired a poor reputation generate new adverse reports. The few controlled clinical studies that have been conducted—including ours—have failed to demonstrate any cardiovascular toxicity of ephedrine (1, 18). Second, although ephedrine has been banned from the US market, it is probably available through illicit channels, through the Internet or as a nondeclared dietary supplement (27), just as similar products are in free trade in other parts of the world. Thus, the safety of these compounds is still relevant.

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