Comparison of Nicotine and Carcinogen Exposure with Water Pipe and Cigarette Smoking

Peyton Jacob III1, Ahmad H. Abu Raddaha2, Delia Dempsey1, Christopher Havel1, Margaret Peng1, Lisa Yu1, and Neal L. Benowitz1

Abstract

Background: Smoking tobacco preparations in a water pipe (hookah) is widespread in many places of the world and is perceived by many as relatively safe. We investigated biomarkers of toxicant exposure with water pipe compared with cigarette smoking.

Methods: We conducted a crossover study to assess daily nicotine and carcinogen exposure with water pipe and cigarette smoking in 13 people who were experienced in using both products.

Results: When smoking an average of 3 water pipe sessions compared with smoking 11 cigarettes per day (cpd), water pipe use was associated with a significantly lower intake of nicotine, greater exposure to carbon monoxide (CO), and a different pattern of carcinogen exposure compared with cigarette smoking, with greater exposure to benzene, and high molecular weight polycyclic aromatic hydrocarbon (PAH), but less exposure to tobacco-specific nitrosamines, 1,3-butadiene, acrolein, acrylonitrile, propylene oxide, ethylene oxide, and low molecular weight PAHs.

Conclusions: A different pattern of carcinogen exposure might result in a different cancer risk profile between cigarette and water pipe smoking. Of particular concern is the risk of leukemia related to high levels of benzene exposure with water pipe use.

Impact: Smoking tobacco in water pipes has gained popularity in the United States and around the world. Many believe that water pipe smoking is not addictive and less harmful than cigarette smoking. We provide data on toxicant exposure that will help guide regulation and public education regarding water pipe health risk. Cancer Epidemiol Biomarkers Prev; 22(5); 765–72. ©2013 AACR.

Introduction

It is estimated that about 100 million people worldwide smoke tobacco in water pipes. Water pipe is also known as hookah (Indian subcontinent and Africa), shisha, borry, goza (Egypt and Saudi Arabia), narghile, arghile (Jordan, Lebanon, Syria, and Israel), shui yan dai (China), or hubble-bubble (1, 2). Smoking tobacco in water pipes has gained popularity in the United States, particularly in areas with sizable Arab-American populations, and also among young non–Arab-American people, with hookah bars often being located near college campuses (3). A typical session at a hookah bar involves smoking for 45 to 60 minutes, often with a group of friends (4–6). Many believe that water pipe smoking is not addictive and is less harmful than cigarette smoking (1, 5, 7).

A water pipe consists of a head that is connected to a bowl containing water and a hose with mouthpiece. A tobacco preparation is placed in the head and burning charcoal is placed on top of the tobacco. The smoker inhales through a mouthpiece, which draws air and hot combustion products from the burning charcoal through the tobacco preparation, creating an aerosol consisting of volatilized and pyrolyzed tobacco components. The smoke passes through the water in the bowl, cooling the smoke, before being carried through the hose to the smoker.

Water pipe tobacco is a moist paste-like preparation made from about 5% to 10% crude cut tobacco that is fermented with honey, molasses, and pulp of different fruits to add flavor. Differences in composition of the products smoked and different temperatures involved in the smoking process result in substantial difference in the composition of hookah smoke compared with cigarette smoke. Water pipe smoke is produced at about 450°C compared with about 900°C for cigarettes (8). Furthermore, water pipe smoke also contains charcoal combustion products, including substantial amounts of carbon monoxide (CO).

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On the basis of smoking machine data, the amount of water pipe tobacco used in a single smoking session was reported to produce 100-fold more tar, 4-fold more nicotine, 11-fold more CO, and 2- to 5-fold more polycyclic aromatic hydrocarbons than did a single cigarette (8). Other investigators have confirmed these findings, but polycyclic aromatic hydrocarbon (PAH) delivery was higher for some PAHs and lower for others (9). Shafagoj and colleagues found that the water pipe smokers had about 2-fold higher expired CO levels and about 3-fold higher plasma nicotine levels than cigarette smokers (10). We recently studied biomarkers of nicotine and carcinogen exposure after single water pipe sessions and found that peak plasma nicotine concentrations were comparable and expired CO levels were much higher than those typically seen after smoking a cigarette (11). We found that the estimated systemic dose of nicotine from one session of water pipe smoking was similar to smoking 2 to 3 cigarettes, and water pipe smoking significantly increased urine excretion of tobacco-specific nitrosamines and PAHs, representing 2 major classes of tobacco smoke carcinogens (12).

The goal of the present study was to compare toxicant exposure from water pipe smoking with exposure from cigarette smoking using biomarker measurements. We conducted a crossover study to assess daily nicotine and carcinogen exposure with water pipe and cigarette smoking in people who were experienced users of both products.

Materials and Methods

Subjects

Thirteen healthy volunteers who smoked both cigarettes and water pipes completed the study. They included 8 men and 5 women, 8 non-Hispanic whites, 1 Hispanic white, 3 Asians, and 1 African-American with a mean age of 24 years (range 18–33 years) and an average body mass index (BMI) of 26 (range 21–35). Subjects smoked an average of 10 cigarettes per day (cpd; range 4–20) and had an average Fagerström Test of Nicotine Dependence score of 3 (range 0–6). Subjects reported smoking an average of 3 water pipe sessions per week (range 1–7) for an average of 4.8 years (range 1.5–7 years). The average saliva cotinine at screening was 72 ng/mL (range 20–150).

Participants were recruited through Internet postings (Craigslist) and word of mouth. Subjects were financially compensated for their time. The study was approved by the Committee on Human Research at University of California, San Francisco (San Francisco, CA).

Study procedures

This was a randomized, 2 arm, crossover study of water pipe and cigarette smoking. The arms comprised exclusive water pipe smoking and exclusive cigarette smoking, each requiring 4 inpatient days in the Clinical Research Center (CRC) at San Francisco General Hospital (San Francisco, CA), with at least 1 week separating each arm. Randomization of the sequence of treatment arms was done separately for males and females. Subjects were requested to refrain from smoking from 9:00 pm on the night before CRC admission, which occurred at 7:00 am the next day. On each hospital day, subjects were required to have their first smoking session (cigarette or water pipe) at 9:00 am. This was to maintain the same day–night tobacco use schedule throughout. A 24-hour urine was collected daily, with a split urine collection on day 4 as described below.

Subjects were allowed to smoke cigarettes as desired between 9:00 am and 10:00 pm (CRC policy). Subjects were required to smoke the water pipe for a minimum of twice per day (9:00 am and 1:00 pm), but otherwise could smoke water pipe ad libitum between 9:00 am and 6:00 pm. Evening water pipe smoking was not allowed because the kitchen, where the charcoal was lighted, closes at 6:00 pm. The following were recorded daily, depending on the study arm: CPD number and weight of cigarettes smoked or weight of water pipe tobacco smoked, times, duration, and number of sessions. Each day, the water in the pipe was replaced (825 mL), and at the end of the day, a water sample was retained for nicotine analysis.

Subjects were intensively studied on the fourth hospital day of each hospital stay. A blood sample was collected and expired CO recorded before and 2 minutes after completing the first smoking session at 9:00 am and again after another smoking session at 1:00 pm. Additional blood and expired CO samples were collected at 7, 9, 11, 13, and 24 hours from the start of the first smoking session. To examine the time course of excretion of toxicants, urine was collected at intervals of 0–4, 4–8, 8–12, and 12–24 hours.

The U.S. Federal Trade Commission method machine-determined yields of the usual cigarette brands averaged 1.07 mg (SD, 0.37) nicotine, 13.0 mg (2.9) tar, and 13.1 mg (1.0) CO. The self-selected water pipe tobacco brands and flavors smoked during the water pipe arm of the study are: Nakhla Double Apple; Nakhla Strawberry; Nakhla Mango (2 subjects); Nakhla Apple (3 subjects); Nakhla Peach (3 subjects); Al-Waha Peach; and Al-Waha 2-Apple (2 subjects).

Laboratory analysis

Biomarkers of exposure to several toxic substances were measured (Table 1). Analyses of biofluid samples were carried out using published methods (13–15) or are described in the Supplementary Materials Section.

Statistical analysis

Area under the plasma nicotine concentration–time curve (AUC) and expired CO AUC were the primary measures of daily nicotine and CO exposure, respectively. The 24-hour excretion of various smoke toxin metabolites was used as the measure of these toxicant exposures. On the basis of common practice, data are presented in "pmol/24 h" for plasma nicotine, "ppm" for expired CO, "pmol/24 h" for 4-(methylnitrosamo)-1-(5-pyridyl)-1-
Table 1. Urinary excretion of toxic substance biomarkers \(^a\)

<table>
<thead>
<tr>
<th>Toxic substance</th>
<th>Biomarker</th>
<th>Water pipe</th>
<th>Cigarette</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study day 3</td>
<td>Study day 4</td>
<td>Average</td>
</tr>
<tr>
<td>NNK</td>
<td>NNAL</td>
<td>226 (136–373)</td>
<td>210 (137–319)</td>
</tr>
<tr>
<td>(TSNA)</td>
<td>(pmol/24 h)</td>
<td>328 (119–447)</td>
<td>226 (110–336)</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>2-Naph</td>
<td>3,844 (2,649–5,574)</td>
<td>3,174 (2,234–4,524)</td>
</tr>
<tr>
<td>(PAH)</td>
<td>(pmol/24 h)</td>
<td>3,383 (2,270–5,653)</td>
<td>3,513 (2,094–5,607)</td>
</tr>
<tr>
<td>Fluorene</td>
<td>1-Fluor</td>
<td>96 (52–178)</td>
<td>90 (52–158)</td>
</tr>
<tr>
<td>(PAH)</td>
<td>(pmol/24 h)</td>
<td>235 (39–273)</td>
<td>143 (44–187)</td>
</tr>
<tr>
<td>Fluorene</td>
<td>2-Fluor</td>
<td>65 (29–146)</td>
<td>135 (59–309)</td>
</tr>
<tr>
<td>(PAH)</td>
<td>(pmol/24 h)</td>
<td>195 (18–212)</td>
<td>370 (36–406)</td>
</tr>
<tr>
<td>Fluorene</td>
<td>3-Fluor</td>
<td>54 (36–82)</td>
<td>49 (35–68)</td>
</tr>
<tr>
<td>(PAH)</td>
<td>(pmol/24 h)</td>
<td>65 (31–96)</td>
<td>40 (33–72.6)</td>
</tr>
<tr>
<td>Phanethrene</td>
<td>Sum of Phen</td>
<td>361 (241–537)</td>
<td>335 (242–462)</td>
</tr>
<tr>
<td>(PAH)</td>
<td>(pmol/24 h)</td>
<td>331 (201–533)</td>
<td>300 (203–503)</td>
</tr>
<tr>
<td>Pyrene</td>
<td>1-HP</td>
<td>117 (85–160)</td>
<td>109 (83–144)</td>
</tr>
<tr>
<td>(PAH)</td>
<td>(pmol/24 h)</td>
<td>127 (80–206)</td>
<td>109 (70–179)</td>
</tr>
</tbody>
</table>

| Ethylene Oxide | HEMA      | 3.47 (2.45–4.91) | 5.97 (3.64–9.8) | 0.01 |
| (VOC)          | (\(\mu\)g/24 h) | 2.38 (2.48–4.88) | 8.58 (2.97–11.55) | -0.01 |
| Acrylonitrile  | CNEMA     | 14.3 (8.3–24.8) | 70.9 (45.4–10.9) | -0.01 |
| (VOC)          | (\(\mu\)g/24 h) | 18.7 (8.9–27.4) | 90.1 (43–133.1) | -0.01 |
| Acrolein       | 3-HMPA    | 418.6 (227.2–535.7) | 601.6 (450.8–802.8) | 0.01 |
| (VOC)          | (\(\mu\)g/24 h) | 152.6 (37.6–490.2) | 388.6 (425.3–814) | -0.01 |
| Propylene Oxide| 2-HMPA    | 59.4 (34.9–101) | 94.9 (55.4–162.7) | 0.04 |
| (VOC)          | (\(\mu\)g/24 h) | 80.3 (28.7–109) | 148.1 (50.2–198.2) | -0.01 |
| 1,3-Butadiene  | MHBMA     | 0.39 (0.3–0.52) | 1.3 (1.02–1.65) | 0.2 |
| (VOC)          | (\(\mu\)g/24 h) | 0.28 (0.27–0.55) | 0.76 (0.96–1.72) | -0.01 |
| Acrylamide     | AAMA      | 105.8 (74.3–150.5) | 132.7 (99.5–177) | -0.01 |
| (VOC)          | (\(\mu\)g/24 h) | 44.1 (77.7–121.8) | 84.4 (66.8–181.2) | -0.01 |
| Benzene        | PMA       | 1.73 (0.76–3.03) | 0.695 (0.39–1.25) | 0.03 |
| (VOC)          | (\(\mu\)g/24 h) | 5.67 (0.49–16.6) | 0.75 (0.35–1.09) | -0.01 |

Note: Significant differences are in bold. Mercapturic acid metabolites of volatile organic chemicals were measured on day 4 only, so there are no day 3 or average data for these analytes.

Abbreviations: AAMA, 2-carbamoylmercapturic acid; CNEMA, 2-cyanethylmercapturic acid; 1-Fluor, 1-hydroxyfluorene; 2-Fluor, 2-hydroxyfluorene; 3-Fluor, 3-hydroxyfluorene; HEMA, 2-hydroxyethylmercapturic acid; 1-HP, 1-hydroxyphenanthrene; 2-HPMA, 2-hydroxypropylmercapturic acid; 3-HPMA, 3-hydroxypropylmercapturic acid; MHBMA, 2-hydroxynaphtho-3-buten-1-ylmercapturic acid or isomer(s); 2-Naph, 2-naphthol; PMA, phenylmercapturic acid; Sum of Phen, sum of 1-, 2-, 3-, and 4-hydroxyphenanthrenes.

\(^a\)All values are presented in this format: geometric mean (95% confidence interval of geometric mean) on the top line and median (interquartile interval) on the bottom line.
butanol (NNAL) and PAH metabolites, and in “μg/24 h” for mercapturic acids.

Differences between water pipe and cigarette smoking were analyzed using paired Student t tests. Because the data were not normally distributed, log transformation of the data was conducted. NNAL and PAH urine values were averaged on study days 3 and 4. Mercapturic acid metabolite data were available only on day 4. Two-tailed tests with α = 0.05 were used. Data analysis was conducted using IBM SPSS 18 for Windows, 2009.

Results

Biomarkers of exposure to several toxic substances were measured. These included nicotine, CO, NNAL, a metabolite of the lung-selective carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), biomarkers for the PAH class of carcinogens, and mercapturic acid metabolites of several toxic volatile organic compounds (VOC; ref. Table 1).

On average, subjects smoked water pipe for 2.8 (SD, 0.7; range 2–4) sessions with a total of 45.8 (SD, 9.7; range 28.5–60) minutes of smoking and smoked 11.4 cpd (SD, 6.3; range 3.5–21). The average nicotine concentration in the water after smoking water pipe was 4.5 μg/mL (SD 3.7).

The average total nicotine remaining in the water per water pipe session was 1.22 mg (SD 0.76); the average nicotine remaining per gram tobacco burned was 0.21 mg (SD 0.10).

Average plasma nicotine and expired CO concentrations on study day 4 are shown in Fig. 1A and B. Average plasma nicotine concentrations throughout day 4 were substantially lower during water pipe use compared with cigarette smoking even though the mean plasma nicotine boost for the 2 individual smoking sessions was not significantly different for water pipe (11.4 ng/mL) compared with cigarette smoking (9.2 ng/mL). The 24-hour AUC for nicotine, an integrated measure of exposure, was significantly lower for water pipe [63.9 ng/mL/C2h (SD 50)] compared with cigarette smoking [127.4 ng/mL/C2h (SD 81)] (P < 0.01). The average CO boost after smoking water pipe was 86 ppm compared with 5.2 ppm after cigarette smoking (P < 0.001). The mean 24-hour AUC for expired CO was 903 ppm/C2h for water pipe and 335 ppm/C2h (SD 442) for cigarette smoking (P < 0.05).

Urine NNAL levels were significantly lower during water pipe use compared with cigarette smoking (Fig. 2A, Table 1). Relative excretion of different PAH metabolites varied according to the type of tobacco. Average excretion of 2-naphthol and 1, 2, and 3-hydroxyfluorenes was significantly higher in cigarette smokers, whereas excretion of 1-hydroxypyrene was significantly higher with water pipe smoking (Table 1). The sum of hydroxyphenanthrene excretion was similar for both groups.

Relative urine excretion of different VOC metabolites varied according to the mode of smoking and type of tobacco (Table 1). Excretion of phenylmercapturic acid (metabolite of benzene) was significantly higher with water pipe use compared with cigarette smoking (Fig. 3A). Excretion of 2-hydroxyethylmercapturic acid, 2-cyanoethylmercapturic acid, 2-hydroxypropylmercapturic acid, 2-hydroxypropylmercapturic acid, and 2-hydroxy-3-buten-1-yl-mercapturic acid and isomer(s) (metabolites of ethylene or ethylene oxide, acrylonitrile, acrolein, propylene or propylene oxide, and 1,3-butadiene, respectively) were significantly higher during cigarette smoking (1,3-butadiene metabolite data shown in Fig. 3B). There was no significant difference in the excretion of 2-carboxymethylmercapturic acid (acrylamide metabolite)

A significant increase in heart rate was observed both after smoking cigarettes (11.2 bpm, P = 0.011) and water pipe (11.6 bpm, P < 0.001). Systolic blood pressure...
increased after cigarette (9.7 mmHg, \( P = 0.01 \)) and water pipe smoking (8.0 mmHg, \( P = 0.026 \)); the changes were not significantly different comparing cigarettes versus water pipe.

**Discussion**

Because many people believe water pipe smoking is less harmful than cigarette smoking, and the chemistry of the 2 smoking processes is quite different, a study comparing the intake of toxic substances in people who customarily smoke both of these 2 products was warranted. To the best of our knowledge, this is the first study to compare cigarette smoking with water pipe smoking using a cross-over protocol. The study involved a steady-state assessment of biomarkers of systemic exposure to tobacco smoke toxicants during *ad libitum* smoking (the exception being NNAL, which has a 10–16 day half-life) (17) compared with *ad libitum* water pipe smoking. The pattern of toxicant exposure was distinctly different for water pipe smoking as compared with cigarette smoking. We made several novel and significant findings related to assessment of nicotine, CO, and 3 classes of carcinogens as follows.

**Nicotine exposure and effects**

Daily nicotine intake, estimated on the basis of 24-hour AUC, was substantially higher while smoking cigarettes compared with water pipe. Nonetheless, the sustained levels of nicotine throughout most of the day with water pipe use are likely to cause physiologic changes in the brain that would sustain nicotine addiction (18). Heart rate acceleration and an increase in systolic blood pressure are well-described pharmacologic effects of nicotine and were similar in our study after water pipe and cigarette smoking. Similar cardiovascular findings have been reported by Hakim and colleagues (19).

Previously, we reported that the 12.5 gm of water pipe tobacco placed in the pipe contained, on an average, 32 mg nicotine, and the average systemic intake of nicotine was 2.6 mg per water pipe session (11). We found in the present study that only 1.2 mg nicotine on average was recovered in the water pipe water per session, representing about 4% of nicotine in 12.5 gm of water pipe tobacco. Given that nicotine is highly water soluble, the relatively low nicotine recovery in the water is likely explained by most nicotine being carried through the water in air bubbles, with little time for dissolution. This finding contrasts to beliefs of...
some water pipe smokers that the water removes harmful substances.

**Tobacco-specific nitrosamines**

Although not at steady-state, levels of the tobacco-specific nitrosamines (TSNA) biomarker NNAL, reflecting systemic exposure to the lung carcinogen NNK, were much lower during water pipe smoking compared with cigarette smoking. Lower levels of urine NNAL have been previously reported in Egyptian water pipe compared with cigarette smokers (20). This might be due to differences in the tobacco type or curing process used to manufacture the products or it might be due to reducing agents, such as ascorbic acid (21) in the fruit preparation inhibiting formation of TSNA during curing or in storage.

**Polycyclic aromatic hydrocarbons**

Intake of naphthalene and fluorene was higher during cigarette smoking, but intake of phenanthrene and pyrene was higher during water pipe smoking. This trend suggests that there may be a continuum with higher molecular weight PAHs being more abundant in water pipe smoke than in cigarette smoke. Because higher molecular weight PAHs are generally the most carcinogenic (e.g., benzo[a]pyrene and benz[a]anthracene), this trend suggests that cancer risk from PAHs might be higher in water pipe smokers than in cigarette smokers.

**Volatile Organic Compounds**

Exposure to benzene, a proven human carcinogen (leukemia and possibly lung cancer) (1) was considerably higher while smoking water pipe compared with cigarettes. This was surprising in light of the trend for PAHs of higher molecular weight being higher in water pipe smoke. It may be that the burning charcoal is a major source of benzene (22). In contrast, intake of some other toxic VOCs, 1,3-butadiene, ethylene oxide, acrolein, acrylonitrile, and propylene oxide was higher during cigarette smoking. Both 1,3-butadiene and ethylene oxide are considered carcinogenic in humans (class 1), (1, 23). Acrolein, an irritant and ciliotoxic chemical, is carcinogenic in animals and is thought to play a major role in tobacco-induced cardiovascular disease (24). Acrylonitrile and propylene oxide are class 2B carcinogens (1). Thus, the profile of VOC exposure differs in water pipe and cigarette smokers, which may have implications for different disease risks. The different pattern of VOC exposure is likely due to the different composition of the products and differences in the smoking process. The water pipe product is mostly a moist fruit preparation containing about 5% to 10% tobacco, and is not combusted, but rather heated to the point of charring by burning charcoal placed on top of it. Thus, the temperature at which pyrolytic chemistry and aerosol formation occur is considerably lower in water pipe smoking (~ 450°C) as compared with cigarette smoking (~ 900°C) (8).

**Carbon monoxide**

As reported in previous studies (11, 25), CO intake was much higher while smoking water pipe, probably because burning charcoal is placed on top of the fruit-tobacco mixture to volatilize substances in the product and generate an inhalable aerosol. CO reduces the oxygen carrying and delivering capacity of the blood. High CO levels are particularly hazardous in people with ischemic cardiovascular disease and chronic obstructive lung disease, where CO exposure reduces the exercise capacity and increases the risk of potentially fatal cardiac arrhythmias (26, 27).

Limitations of our study warrant discussion. First, we studied dual users, that is, people who regularly smoke both cigarettes and water pipe, so that we could conduct a crossover study. Our prior research suggested that dual users inhale water pipe more intensively and are exposed to higher levels of tobacco smoke toxicants compared with water pipe-only users (11). Second, we studied subjects who smoked their products on a clinical research ward, by themselves. Much water pipe use is social and involves sharing of a water pipe with friends. For these reasons, our
estimates of exposure to tobacco smoke toxicants from water pipe are likely to be more than that experienced by many social water pipe smokers. Third, the smoking patterns for both water pipe and cigarettes on the research ward were constrained by experimental design (first cigarette at 9 am) and by ward policy (no water pipe after 6 pm or cigarettes after 10 pm). Thus, the exposures that we estimated may be less than that would have occurred with ad libitum smoking in a natural environment.

In conclusion, when toxicant exposures in the same individuals were compared while smoking an average of 3 water pipe sessions versus smoking 11 cigarettes per day, differences in product composition and in the smoking processes resulted in different patterns of exposure to various tobacco toxicants. Water pipe use was associated with less nicotine intake than cigarette smoking, but with levels likely to be capable of sustaining addiction. There was a greater exposure to benzene and high molecular weight PAHs, but less exposure to 1,3-butadiene, acrolein, acrylonitrile, propylene oxide, ethylene oxide, and low molecular weight PAHs. This might result in a different clinical cancer risk profile between cigarette and water pipe smoking. Epidemiologic studies have reported associations between water pipe smoking and increased risks of lung cancer, respiratory illness, low birth weight, and periodontal disease (28). However, these studies have limitations and reflect exposure to many different types of water pipe products. We are aware of no data on water pipe smoking and the risk of leukemia, which is of interest as benzene exposure is a risk factor in this disease. CO levels with regular water pipe use are extraordinarily high and could pose a risk to health in people with underlying cardiovascular or pulmonary disease. With regular daily use, water pipe smoking is not a safe alternative to cigarette smoking, nor is it likely to have an effective harm.

Disclosure of Potential Conflicts of Interest
N.L. Benowitz has provided expert testimony in tobacco litigation related to nicotine addiction from the past 5 years. No potential conflicts of interest were disclosed by the other authors.

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Study supervision: D. Dempsey

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