Deaths Attributable to Methadone vs Buprenorphine in France

Marc Auriacombe; Pascale Franques; Jean Tignol


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Oral Contraceptives and Risk of Breast Cancer in Women With a Family History of Breast Cancer

To the Editor: Ms Grabrick and colleagues\(^1\) suggest that the risk of breast cancer from oral contraceptive (OC) use is related to estrogen use. They state, “The amount of estrogen in OCs has decreased from an initial 130 µg to 50 µg or less currently. . . .” However, the original 1960s “pill,” Enovid, contained many times that amount of estrogen. I can find no studies on the risk of breast cancer from Enovid use. If the risk is in fact dose-related, that would seem an obvious “natural experiment.”

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To the Editor: The findings of Ms Grabrick and colleagues\(^1\) strengthen the results of previous studies showing that women who have used OCs and have a family history (first degree female relative) of breast cancer may be at higher risk of developing breast cancer themselves. However, because recall bias is inevitable with such a long follow-up (>35 years), I do not agree with the authors that the reliability of the data was greater than 90%. Surveillance bias may have similarly limited the study’s validity. Also, concomitant smoking and OC use may have exerted confounding effects. A recent report shows an increased breast cancer risk in patients with a history of both active and passive smoking.\(^2\) Another study also suggests a modest increase in breast cancer risk associated with adolescent smoking.\(^3\)

The risk of breast cancer and the use of OCs in carriers of BRCA1 and BRCA2 mutations has not yet been determined. In addition, because of changes in estrogen and progesterone levels in OCs since 1975, further studies need to be done to see if there are true dose-related effects on breast cancer with currently available OCs. Until then, clinicians should be cautious in prescribing OCs to patients who have risk factors such as smoking or a first degree relative with a history of breast cancer.

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In Reply: Dr Kirkland raises an important issue regarding OC formulations, like Enovid, that contained especially high doses of estrogens. The problem, from an epidemiologic perspective, is the accuracy of recall about specific brands and formulations. Recent research has found that women are able to recall ever or never use and age of use, but not specifics—even when prompted with picture cards of possible brands.\(^1,2\) Thus, we made no attempt to obtain such specific information. We agree, however, that such detailed information could help clarify this important issue.

Drs Aslam and Rashid raise questions regarding recall bias, surveillance bias, and adjustment for smoking. Although recall bias is an important issue, it is difficult to validate such exposures in the context of a historical cohort study with extended follow-up. However, the literature on validity of OC recall suggests that subjects can provide accurate historical information with little evidence for bias by case or control status.\(^1,3\) Regarding surveillance bias, we agree that women receiving OCs may have greater contact with health care providers than those who do not. Since we did not have direct data on access to health care, we used mammography utilization as a surrogate. The degree of utilization factor did not completely account for our findings.

We agree that smoking is an important potential confounder, especially since it has been reported that smoking is protective against breast cancer among women carrying mutations in BRCA1 or BRCA2.\(^3\) However, we have found that smoking increases the risk of breast cancer in these families.\(^4\) Aslam and Rashid are concerned about concurrent exposure to smoking and OCs. Several observations may be pertinent here. First, in our sample, ever use of OCs was more common among smokers than never-smokers (68% vs 44%). Second, 90% of the women who smoked and used OCs were doing so at the same time. That is, the ages of use overlapped extensively. In

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Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.
addition, the degree of overlap was identical among women who subsequently developed breast cancer (89.8%) and those who did (89.5%). When smoking history was evaluated in our analyses, the association of OCs and breast cancer risk was unchanged; hence, we only presented the simplest models.

Finally, in response to Aslam and Rashid’s point about current formulations, we wish to emphasize that use of OCs marketed after 1975 did not appear to influence risk of breast cancer in our study. However, the power of our study to assess this association was low because of the limited number of women in the exposure category, their young ages, and the limited follow-up.

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Dr Hujoel and colleagues analyzed the First National Health and Nutrition Examination Survey (NHANES I) to assess the relationship between periodontal disease (PD) and coronary heart disease (CHD) and concluded that their study provided “convincing evidence regarding the absence of a moderate-to-large association . . .” between these 2 diseases. We believe that their conclusion about the lack of an association between PD and CHD is premature and unsubstantiated.

Several limitations in the NHANES I data may limit the apparent association between PD and CHD. First, the measure of periodontal disease in NHANES I is subjective and less accurate than objective measures like those used in NHANES III. Hence, misclassification of PD is likely. A longitudinal study1 that used an objective measure of PD showed a strong association between PD and CHD in men.

A further limitation is that PD was measured at baseline only, and changes in periodontal status during the 20-year follow-up were not taken into account. Some of those who had no PD at baseline would be expected to develop the disease later because the prevalence of PD increases markedly with age. Also, the extent of PD in those who already had PD may have been reduced by treatment. Because there are no available data that measure changes over time in periodontal status, the association between PD and CHD might be biased toward the null hypothesis. This issue becomes more problematic as the length of follow-up increases.

Finally, many of the pathophysiologic mechanisms that have been hypothesized as links between PD and CHD relate to the triggering of clinical coronary events. These triggering factors are most significant when they occur close in time to the clinical outcomes; therefore, longitudinal studies may not represent the best study design to investigate these associations.

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In Reply: Dr Genco and colleagues suggest that our conclusion of lack of a moderate-to-large association between PD and CHD is “premature and unsubstantiated.” They are concerned about misclassification bias, long follow-up time with possible dilution effects, and the apparently inconsistent findings of other studies. We respond to each of these criticisms in turn.

Misclassification bias: Genco et al describe our PD measures as “subjective and less accurate” than the objective measures used, for instance, by Beck et al, who showed a “strong association.” However, in a field beset by lack of a standard definition of periodontitis, there is no evidence that our surrogate markers are less accurate or more subjective in measuring PD than the surrogate markers used in studies with positive findings. Furthermore, the odds ratio of 1.5 in the study by Beck et al does not represent a strong association, especially since it was not adjusted for smoking.

Changes in periodontal status during follow-up: While it would be desirable to include longitudinal data on periodontal status, such data are not available. In our study, we investigated whether the estimates of periodontitis-associated CHD hazard changed during the follow-up. No convincing evidence was found (P = .13).

Other studies: The 3 largest studies done to date, including our study, reported the CHD relative risks shown in the Table. The summary relative risk of 1.07, a consistent conclusion of no association across 3 populations, the presence of both short-term and long-term follow-up (addressing the issue of possible dilution effects), the use of different periodontitis measures, and detailed control for confounding variables all argue against a moderate-to-strong association between PD and CHD. A recent meta-analysis, which excluded our study but included underpowered...
Garlic as a Tick Repellent

To the Editor: In their Research Letter, Ms Stjernberg and Dr Berglund documented a repellent effect of garlic against an unnamed species of tick and stated that daily consumption of 1200 mg of garlic was an alternative to “other agents that might have more adverse effects.” Based on the design of their study, any conclusions concerning the relative effectiveness and safety of garlic as a tick repellent are unfounded. They compared garlic to a placebo, but did not present any data on the comparative safety of garlic vs other repellents.

In fact, consumption of garlic appeared to be only marginally better than doing nothing at all to prevent tick bites. By contrast, treatment of clothing with permethrin, a synthetic pyrethroid, has been shown to be 100% effective against *Ixodes scapularis,* the vector of *Borrelia burgdorferi* in the northeastern United States, and to provide nearly 100% protection against *Amblyomma americanum* and *Dermacentor variabilis).* Diethyltoluamide (DEET)-based repellents also are effective in repelling ticks and can be applied to skin, as well as to clothing. The US Department of Defense (DoD) promotes the concurrent use of a 33% DEET-based lotion on exposed skin, treatment of uniforms with permethrin, and proper wearing of the uniform. This strategy has been termed the DoD Repellent System and is believed to be the most effective method for reducing the risk of arthropod bites.

Brown and Hebert were cited as the source of information on adverse effects of repellents other than garlic. In fact, they concluded that appropriate use of repellents was a “safe means of minimizing the risk of bites and vector-borne diseases.” In additional reviews, DEET has been associated with “remarkably few problems” while the concurrent use of DEET and permethrin was judged “safe and effective.”

The study by Stjernberg and Berglund raises 2 additional questions. First, does garlic effectively repel other arthropods of medical importance? Troops frequently are at risk of attack by several arthropod taxa and need a repellent that is broadly effective. The DoD Repellent System is extremely effective in repelling a number of arthropods in addition to ticks. Second, how difficult is it to ensure compliance with a daily regimen of 1200 mg garlic? That is, do troops find garlic acceptable, and can they be relied on to remember to take daily doses? Treatment of uniforms with permethrin can provide repellency for the life of the garment while requiring no action on the part of the wearer. For troops and other populations at high risk for arthropod bites, the use of DEET and permethrin remains the most effective and safe method of protection.

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*CHD indicates coronary heart disease; NHANES I NHEFS, First National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study.*
Thorsell W, Mikiver A, Malander I, Tunoñ H. Efficacy of plant extracts and oils as mosquito repellents. Phytomedicine. Several possible sets of discordant pairs among these projects entering the analysis could therefore be lower, but not greater, receiving either active or placebo treatment. The number of subjects was thus 100. Of these, 66 were reported to have been bitten by ticks. The authors presented a relative risk (RR) of 0.79 with the 95% confidence interval (CI) 0.65-0.96. They did not reveal the number of bitten subjects per sequence. In this trial, a discordant pair is a subject with at least 1 bite while the treatment is the lower ratio between the 2 numbers.

In a crossover trial the RR is calculated from discordant pairs, ie, the number of subjects with more events on active treatment than on placebo is compared with the number of subjects with more events on placebo than on active treatment. The more effective the treatment is the lower ratio between the 2 numbers. In this trial, a discordant pair is a subject with at least 1 bite while receiving either active or placebo treatment. The number of subjects entering the analysis could therefore be lower, but not greater, than 66. Several possible sets of discordant pairs among these 66 conscripts could give a RR of approximately 0.79, but the P value could not be lower than .39 (exact McNemar test using maximum possible sample size, 37 + 29 = 66 discordant pairs). The corresponding CI is 0.46-1.31.

The authors also present a P value of .04 for the difference in number of tick bites between treatments. However, using tick bite as analysis unit instead of conscript is incorrect since the risk of a tick bite differs between conscripts; counting tick bites instead of conscripts in a traditional single-level analysis exaggerates the statistical significance of the findings.2


To the Editor: Ms Stjernberg and Dr Berglund1 recently presented a randomized, double-blind, crossover trial of garlic to prevent tick bites among Swedish military conscripts. Fifty subjects were treated with garlic first and placebo second while another 50 were given placebo first and then garlic. The total number of subjects was thus 100. Of these, 66 were reported to have been bitten by ticks. The authors presented a relative risk (RR) of 0.79 with the 95% confidence interval (CI) 0.65-0.96. They did not reveal the number of bitten subjects per sequence. In a crossover trial the RR is calculated from discordant pairs, ie, the number of subjects with more events on active treatment than on placebo is compared with the number of subjects with more events on placebo than on active treatment. The more effective the treatment is the lower ratio between the 2 numbers. In this trial, a discordant pair is a subject with at least 1 bite while receiving either active or placebo treatment. The number of subjects entering the analysis could therefore be lower, but not greater, than 66. Several possible sets of discordant pairs among these 66 conscripts could give a RR of approximately 0.79, but the P value could not be lower than .39 (exact McNemar test using maximum possible sample size, 37 + 29 = 66 discordant pairs). The corresponding CI is 0.46-1.31.

The authors also present a P value of .04 for the difference in number of tick bites between treatments. However, using tick bite as analysis unit instead of conscript is incorrect since the risk of a tick bite differs between conscripts; counting tick bites instead of conscripts in a traditional single-level analysis exaggerates the statistical significance of the findings.2


In response to Dr McHugh, our study specifically assessed the effectiveness of garlic as a repellent for tick bites. We did not measure its effectiveness for other arthropods or insects, nor did we compare it with other repellents. We choose military personnel because their behavior is relatively consistent.

Both McHugh and Dr Tunoñ point out that there are other effective insecticides and repellents. However, the adverse effects of DEET and permethrin are a subject of recurrent debate. Swedish regulations concerning the use of these products are very strict, for permethrin because of toxicity in aquatic organisms1 and for DEET because of studies showing adverse effects in humans.2,3 Thus, Swedish troops cannot use permethrin- or DEET-treated uniforms. In Sweden, garlic might be considered as an alternative to other repellents for people staying in tick endemic areas. Of course, treatment of clothes with permethrin guarantees a much higher level of protection as long as the clothing are worn. Garlic should certainly not be substituted for more effective protective measurements in areas that are endemic to other vector borne diseases, such as malaria.

In response to Dr Ranstam, all participants in our trial recorded in a diary the time of exposure and observed tick bites. This allowed us to standardize for time of exposure. Our statements were related to per protocol analysis only, which lead us to be conservative in our conclusions. Per protocol statements included all individuals fulfilling the study requirements and describes the time the study drug was taken as directed; all episodes with deviating compliance were excluded.

The 2 periods of observation differed in length, and some units spent different amounts of time within each period. Therefore, we considered the Wilcoxon test for paired observations a more appropriate method to test our hypothesis. This test for paired samples compared the individual number of tick bites per unit of time (days) between placebo and active treatment. However, when presenting the RRs we compared (standardized for time of exposure) the number of bitten participants in the placebo groups with the number of bitten participants in the garlic groups and did not take into consideration the crossover design when comparing paired samples. We agree that this is inappropriate and that CIs should not have been presented.

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Preventing Vibrio parahaemolyticus Infection

In Reply: In response to Dr Daniels and colleagues,1 described a 1998 outbreak of Vibrio parahaemolyticus that resulted from consumption of raw oysters. We wish to provide information on...
control strategies that have been put in place since the 1998 events summarized in that article.

Routine bacteriological monitoring failed to prevent the outbreak for 2 reasons. First, the bacteriological monitoring of environmental waters conducted routinely by states at harvest sites was aimed solely at preventing hazards transmitted by fecal contamination, such as Salmonella bacteria, and not those posed by environmental bacterial species, such as *V parahaemolyticus*. Second, it was not until the 1997 and 1998 shellfish-borne outbreaks caused by *V parahaemolyticus* that shellfish control authorities in the United States recognized the need for separate monitoring programs and prevention plans to address outbreaks caused by *V parahaemolyticus* in shellfish.

As a result of the 1998 outbreak and a smaller outbreak in the Pacific Northwest in 1997, the US Food and Drug Administration (FDA) advised the Interstate Shellfish Sanitation Conference (ISSC) of the need to prescribe monitoring for *V parahaemolyticus*. The FDA also provided guidance and recommendations to the ISSC for such monitoring. In 1999, the ISSC unanimously approved a new interim control plan that prescribes monitoring oysters specifically during periods of the year known to be associated with the occurrence of *V parahaemolyticus* in those states where outbreaks and sporadic cases have occurred. Harvest waters implicated by detection of pathogenic *V parahaemolyticus* through monitoring programs are closed for the harvesting of shellfish until monitoring indicates the pathogen is no longer detectable. This strategy is intended to prevent shellfish-borne outbreaks caused by this organism. If an outbreak does occur, the implicated harvest waters are closed for harvesting until monitoring indicates the pathogen is no longer detectable or until environmental temperatures become unfavorable for the proliferation of this organism.

Since 1998, the US Centers for Disease Control and Prevention (CDC) also increased surveillance of *V parahaemolyticus* infections. This surveillance indicates that the outbreak-related strain has not disappeared. To date, however, no oyster-related outbreaks of *V parahaemolyticus* infections have been recognized since 1998.

The FDA, CDC, and ISSC are committed to addressing the problem of *V parahaemolyticus* associated with molluscan shellfish. As in the past, an outbreak of shellfish-borne *V parahaemolyticus* infection will lead to a prompt reevaluation and, as necessary, a revision of policy.

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This letter was shown to Dr Daniels and colleagues, who concur with its recommendations.—Ed.

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Disease-Specific Mortality Among Elite Athletes

To the Editor: Studies on the long-term survival of athletes have yielded conflicting results.1,2 We investigated whether the mortality rates of elite athletes varies by participation in different types of sports and how they differ from those of the general population.

Methods. We assessed the mortality of all 2009 male athletes who had represented Finland in international competitions from 1920 to 19653 and were alive in January 1971. Cause-specific deaths from 1971 through 1995 were obtained from Statistics Finland. This database provides virtually complete population mortality data so that cause of death was undefined in only 0.2% of cases. We ranked sports based on average maximal oxygen uptake4 as follows: endurance (highest maximal oxygen uptake), mixed (medium maximal oxygen uptake), and power (lowest maximal oxygen uptake). We computed the standardized mortality ratios (SMRs) for each subgroup of athletes and also compared ratios of the SMRs of the subgroups.

Results. The Table shows the SMRs for cause of death when the mortality in at least 1 specific athlete group was statistically different from the mortality in the general population. All-cause SMRs were low among the athletes generally, particularly for those with high or medium oxygen uptake (the endurance and mixed sports groups). The SMRs for coronary heart disease were low for endurance and mixed sports athletes but not for power athletes; SMRs for pulmonary diseases were low for endurance and mixed sports groups. The SMRs for coronary heart disease mortality data so that cause of death was undefined in only 0.2% of cases. We ranked sports based on average maximal oxygen uptake as follows: endurance (highest maximal oxygen uptake), mixed (medium maximal oxygen uptake), and power (lowest maximal oxygen uptake). We computed the standardized mortality ratios (SMRs) for each subgroup of athletes and also compared ratios of the SMRs of the subgroups.

Results. The Table shows the SMRs for cause of death when the mortality in at least 1 specific athlete group was statistically different from the mortality in the general population. All-cause SMRs were low among the athletes generally, particularly for those with high or medium oxygen uptake (the endurance and mixed sports groups). The SMRs for coronary heart disease were low for endurance and mixed sports athletes but not for power athletes; SMRs for pulmonary diseases were low for endurance and mixed sports groups. The SMRs for coronary heart disease mortality were lower among endurance athletes than power athletes. Thus, differences in biological characteristics between endurance and power athletes may explain the selection of specific types of sports as well as some of the differences in risk of developing coronary heart disease that has been previously reported.

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Heikki O. Tikkanen, MD, PhD
Unit for Sports and Exercise Medicine,
Institute of Clinical Medicine

Table. Standardized Mortality Ratios of Elite Finnish Male Athletes Compared With the General Population by Cause of Death and Type of Sport*

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Observed Deaths</th>
<th>Expected Deaths</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endurance sports†</td>
<td>108</td>
<td>189.34</td>
<td>0.57 (0.47-0.68)</td>
</tr>
<tr>
<td>Mixed sports‡</td>
<td>292</td>
<td>427.31</td>
<td>0.68 (0.61-0.76)</td>
</tr>
<tr>
<td>Power sports§</td>
<td>337</td>
<td>373.88</td>
<td>0.90 (0.81-1.00)</td>
</tr>
<tr>
<td>Total</td>
<td>737</td>
<td>990.53</td>
<td>0.74 (0.69-0.79)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(acute myocardial infarction and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other ischemic heart disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endurance sports†</td>
<td>36</td>
<td>64.81</td>
<td>0.56 (0.39-0.77)</td>
</tr>
<tr>
<td>Mixed sports‡</td>
<td>88</td>
<td>147.12</td>
<td>0.60 (0.48-0.74)</td>
</tr>
<tr>
<td>Power sports§</td>
<td>122</td>
<td>128.41</td>
<td>0.95 (0.79-1.13)</td>
</tr>
<tr>
<td>Total</td>
<td>246</td>
<td>340.34</td>
<td>0.72 (0.64-0.82)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endurance sports†</td>
<td>1</td>
<td>1.37</td>
<td>0.73 (0.02-4.07)</td>
</tr>
<tr>
<td>Mixed sports‡</td>
<td>1</td>
<td>2.94</td>
<td>0.34 (0.01-1.89)</td>
</tr>
<tr>
<td>Power sports§</td>
<td>7</td>
<td>2.66</td>
<td>2.63 (1.06-5.42)</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>6.97</td>
<td>1.26 (0.59-2.45)</td>
</tr>
<tr>
<td>Chronic pulmonary diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(chronic bronchitis, emphysema,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and asthma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endurance sports†</td>
<td>0</td>
<td>7.38</td>
<td>0.00 (0.00-0.49)</td>
</tr>
<tr>
<td>Mixed sports‡</td>
<td>4</td>
<td>14.90</td>
<td>0.27 (0.07-0.68)</td>
</tr>
<tr>
<td>Power sports§</td>
<td>8</td>
<td>13.76</td>
<td>0.58 (0.25-1.14)</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>36.04</td>
<td>0.33 (0.17-0.58)</td>
</tr>
<tr>
<td>Lung cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endurance sports†</td>
<td>2</td>
<td>13.92</td>
<td>0.14 (0.02-0.51)</td>
</tr>
<tr>
<td>Mixed sports‡</td>
<td>12</td>
<td>32.58</td>
<td>0.37 (0.19-0.64)</td>
</tr>
<tr>
<td>Power sports§</td>
<td>13</td>
<td>28.15</td>
<td>0.46 (0.25-0.78)</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>74.65</td>
<td>0.36 (0.24-0.52)</td>
</tr>
</tbody>
</table>

*SMR indicates standardized mortality ratio; CI, confidence interval. SMR is the ratio of observed number of deaths to that expected on the basis of the mortality rates for the Finnish male population standardized for 5-year age groups and 5-year calendar periods.
†Long-distance runners and cross-country skiers; n = 277.
‡Soccer, ice-hockey, basketball, track and field jumpers, and short-distance runners; n = 756.
§Weight-lifters, wrestlers, boxers, and track and field throwers; n = 976.
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Methods. All sudden deaths in France that are thought to be due to use of an illegal substance or misuse of a legal substance are reported to a centralized agency (Office pour la Répression du Trafic Illicite des Stupéfiants). Overdose deaths are calculated based on database evidence and not by laboratory results.

Results. From 1994 to 1998 there were an estimated 1.4 times more buprenorphine-related deaths than methadone-related deaths in France (Table). However, 14 times more patients received buprenorphine than methadone. The yearly estimated death rate related to methadone use was at least 3 times greater than the death rate related to buprenorphine use. If all patients in France who received either of these drugs had been treated only with methadone, the expected number of deaths would have been 288 instead of 46.

Comment. There are several sources of possible inaccuracy in these data, including biases in determination of cause of death and recording. However, we think that such influences would not differentially effect estimates of methadone vs buprenorphine death rates. The large effect size in this population-based estimate suggests that buprenorphine is a safe alternative to methadone, even when prescribed under conditions of increased ease of access.

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Table. Deaths Attributable to Methadone vs Buprenorphine in France, 1994-1998

<table>
<thead>
<tr>
<th>Year</th>
<th>Methadone</th>
<th>Buprenorphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Deaths</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>1994</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>1995</td>
<td>5</td>
<td>400</td>
</tr>
<tr>
<td>1996</td>
<td>3</td>
<td>1200</td>
</tr>
<tr>
<td>1997</td>
<td>7</td>
<td>2350</td>
</tr>
<tr>
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