



# Smoking as a risk factor for accident death: a meta-analysis of cohort studies

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Received 30 October 1998; received in revised form 9 March 1999; accepted 23 March 1999

## Abstract

This meta-analysis discusses the consistency, strength, dose-response, independence, and generalizability of published cohort data on accident death relative risks in smokers. To locate data, three authors independently searched MEDLINE, and bibliographies of the pertinent studies found, for data which allowed estimation of an appropriate cigarette smoker accident death relative risk (and 95% confidence interval). Relative risks and dose-response were summarized by fixed effects and Poisson modeling, respectively. Four pertinent cohort studies including eight populations were located. Cigarette smoking predicted summary accident death relative risks of 1.51 (95% confidence interval 1.27–1.78) versus never smokers and 1.35 (1.17–1.57) versus ex-smokers. Summary dose-response trends were significant ( $P = 0.0000$ ) versus never or least smoking referents. In individual studies, the smoking/accident death association persisted after adjustment or, in effect stratification, for age, race, sex, and occupation: occupation and time period; or numerous cardiac risk factors. This meta-analysis found significant, consistent, dose-response, often strong and independent (of age, race, and sex), prospective associations of smoking with accident death, internationally. Further studies and warnings of the smoking/accident death associations seem merited © 2000 Elsevier Science Ltd. All rights reserved.

*Keywords:* Smoking; Risk factor; Accident death; Meta-analysis

## 1. Introduction

Accidents cause over 90 000 US (Rivara et al., 1997) and three million worldwide deaths annually (World Health Organisation, 1996a,b; World Health Organisation and the World Bank, 1996). Accidents rank fifth among the leading causes of death in the world and probably account for over half (World Health Organisation, 1996a,b; World Health Organisation and the World Bank, 1996) of the 10–30% of all hospital admissions that are due to injury (Berger and Mohan, 1996) and about a third of all deaths ages 10–24 are accidents (World Health Organisation, 1996a,b; World Health Organisation and the World Bank, 1996; Berger and Mohan, 1996). Accidents represent 12% of the global burden of disease (World Health Organisation,

1996a,b; World Health Organisation and the World Bank, 1996).

The World Health Organisation recently recommended that ‘Possible links between... each type of injury and a range of modifiable risk factors... should be quantified’ (World Health Organisation, 1996a,b; World Health Organisation and the World Bank, 1996). In a meta-analysis of smoking and injury, we have shown numerous consistent, dose-response, independent, prospective smoking/injury associations, internationally (Leistikow et al., 1998). We also showed suggestive,  $P = 0.1$  smoking/injury death associations in secondary analyses of randomized controlled trial data (Leistikow and Shipley, 1999).

Smoking directly causes fire, explosion, (Sacks and Nelson, 1994; Leistikow and Martin, 1999) and poisoning accidents (MMWR, 1993; 1997; Hayes and Laws, 1991; Woolf et al., 1996). Smoking may be the leading cause of fire deaths in the West (Whidden and Whidden, 1996).

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It has long been recognized that impaired fitness, e.g. intoxication or debility, may both increase accidents and increase the severity of injuries from accidents that do occur (Haddon, 1980). Smoking is an acknowledged, immense, globally generally increasing, modifiable cause of impaired fitness, including general clinical accident precursors such as debilities, distractions (Sacks and Nelson, 1994), impaired reflexes (Domino and Von Baumgarten, 1969; Wakeham, 1969; Furberg and Ringqvist, 1973), and decrements in physiologic performance (Hirsch et al., 1985; Morton and Holmik, 1985; Perkins et al., 1989; Sandvik et al., 1995), and healing (Kurz et al., 1996; Kwiatkowski et al., 1996). Tobacco industry researchers privately reported nearly 30 years ago that smokers have accident excesses (Wakeham, 1969) and that a dose-response relationship exists between smoking and injury (Dunn, 1969).

The consistency, dose-response, strength, independence, generalizability, and possible importance of associations between smoking and accidents other than motor vehicle accidents have been publicly largely unquantified (Sacks and Nelson, 1994) or unaddressed (Smith et al., 1992; Doll et al., 1994). To quantify the magnitude, dose-response, and characteristics of smoking/accident associations, we will provide a first meta-analysis of smoking and accident death risk in cohort studies.

## 2. Methods

The search, data extraction, and analysis have previously been described in a parallel analysis of smoking/injury (not specifically accident) associations (Leistikow et al., 1998). In brief, MEDLINE and the bibliographies of pertinent retrieved articles were independently searched by three authors using accident or injury, mortality, and cohort or review study type keywords. Two authors independently abstracted the data. Relative risks (RR) were calculated and summarized using RevMan software and a fixed effects analysis, as heterogeneity was not significant across all studies (RevMan, 1998). Dose-response was summarized using Poisson modeling adjusting for person-years of exposure (Leistikow et al., 1998).

Criteria for selection of published studies for meta-analysis were: (1) the ability to extract or estimate person-year based (incidence density) relative risks (RRs) and 95% confidence intervals (CIs) for the association of smoking and accident death (In British physicians and US nurses, accidents were estimated to equal accidents plus homicides, since their homicide numbers are likely to be negligible [Compared to accidents, homicides are rare in Great Britain]. For Californian

nurses, homicide rates were less than one sixth of their accident rates [unpublished data]); (2) The resulting RR was from the longest follow-up for that cohort that we located; (3) The study was published or included in MEDLINE after 1965. (4) The RR were specific to cigarette smoking (as sole use of a pipe or cigars appears to have somewhat different biological effects) (Wald and Watt, 1997).

## 3. Results

Four studies covering eight age-sex specific cohorts met these criteria and are described in Table 1 (Friberg et al., 1973; Hemenway et al., 1993; Kawachi et al., 1993; Tverdal et al., 1993; Doll et al., 1994). (Smoking/injury associations in these and additional cohorts are described elsewhere) (Leistikow et al., 1998). Two papers from the US Nurses Health Study are described as one study as we computed the estimated accident death numbers by subtracting the nurses suicides (Hemenway et al., 1993) from their injury deaths (Kawachi et al., 1993). (We assumed that few homicides had occurred in these nurse volunteers). The included studies all had valid measures of smoking and injury status. The mortality follow-up rates were greater than 93% in each study except, perhaps, the Swedish twins (who presumably had a high follow-up rate due to the Swedish population registries) (Friberg et al., 1973). All studies assessed smoking only at baseline, except Kawachi who used the smoking status recorded at the beginning of each biennium of follow-up (Kawachi et al., 1993) and Doll who used the smoking status at last follow-up (Doll et al., 1994).

Whenever possible, published adjusted RRs are presented in the table in order to show their independence from other factors. Figs. 1 and 2 summarize the associations using crude RR (or estimates there-of [Doll et al., 1994] since crude RRs were most uniformly available, and thus chosen to be summarized). In Figs. 1 and 2, upon meta-analysis, current cigarette smokers demonstrated statistically significant excesses of accident death incidence compared with either people that never smoked (RR = 1.51 [95% confidence interval 1.27–1.78]) or ex-smokers (RR = 1.35 [1.17–1.57]). Heterogeneity was not significant across all studies (including male and female). In the male sub-group alone, heterogeneity was significant compared with ex-smokers (Fig. 2) and substantial compared with people that never smoked (Fig. 1). A dose-response trend, using adjusted data when available (Table 1), from referent, to current lightest, to most heavily cigarette smoking was also present ( $P = 0.0000$ ) versus either never or lightest-smoking referents.

Table 1  
Populations with accident death relative risks included in the summarizations

Author and year	Enrollee, sex and ages	Population studied	Study period	Adjusted/ stratified for	Cigarettes daily	Accident deaths	Person-years	Relative risk	95% C.I. <sup>a</sup>
Doll et al. (1994)	Males, 35–94	British MDs	1951–1991	Age, job, calendar period	Never	78	158 333 <sup>b</sup>	1.0	
					Ex	108	196 429 <sup>b</sup>	1.1	0.8–1.5 <sup>b</sup>
					1–14	61	78 641 <sup>b</sup>	1.6	1.1–2.2 <sup>b</sup>
					15–24	51	88 889 <sup>b</sup>	1.2	0.8–1.7 <sup>b</sup>
					25+	62	54 070 <sup>b</sup>	2.3	1.6–3.3 <sup>b</sup>
Tverdal et al. (1993)	Males, 35–49	Norwegians in five areas	1972–78 to 1988 or emigrate	Age, area	Never	37	127 325	1.0	
					Ex	44	144 776	1.0	0.7–1.7 <sup>b</sup>
					1–9	32	56 350	2.0	0.2–3.2 <sup>b</sup>
					10–19	84	135 167	2.1	1.4–3.2 <sup>b</sup>
					20+	44	56 441	2.7	1.7–4.3 <sup>b</sup>
Friberg et al. (1973)	Males, 35–50	Swedish twin registry, born 1911–25	1961–1972	Crude	Never	9	18 529 <sup>b</sup>	1.0	
					Ex	3	6733 <sup>b</sup>	0.9	0.2–3.7 <sup>b</sup>
					1–10	7	13 445 <sup>b</sup>	1.1	0.3–3.2 <sup>b</sup>
Friberg et al. (1973)	Males, 51–60	Swedish twin registry, born 1901–10	1961–1972	Crude	11+	9	8477 <sup>b</sup>	2.2	0.8–6.2 <sup>b</sup>
					Never	13	9215 <sup>b</sup>	1.0	
					Ex	4	3146 <sup>b</sup>	0.9	0.2–2.9 <sup>b</sup>
Friberg et al. (1973)	Females, 35–50	Swedish twin registry, born 1911–25	1961–1972	Crude	1–10	4	5587 <sup>b</sup>	0.5	0.1–1.6 <sup>b</sup>
					11+	5	2277 <sup>b</sup>	1.6	0.4–4.7 <sup>b</sup>
					Never	10	51 898 <sup>b</sup>	1.0	
Friberg et al. (1973)	Females, 51–60	Swedish twin registry, born 1900–10	1961–1972	Crude	Ex	0	3382 <sup>b</sup>	0.0	0.0–6.8 <sup>b</sup>
					1–10	3	12 071 <sup>b</sup>	1.3	0.2–5.0 <sup>b</sup>
					11+	1	3473 <sup>b</sup>	1.5	0.0–10.5 <sup>b</sup>
Friberg et al. (1973)	Females, 30–55	US Nurses' health study, 98% white	1976–1988	Age, job	Never	8	29 864 <sup>b</sup>	1.0	
					Ex	1	895 <sup>b</sup>	4.2	0.1–31.1 <sup>b</sup>
					1–10	1	3056 <sup>b</sup>	1.2	0.0–9.1 <sup>b</sup>
Kawachi et al. (1993) and Hemenway et al. (1993)	Females, 30–55	US Nurses' health study, 98% white	1976–1988	Age, job	11+	0	765 <sup>b</sup>	0.0	0.0–22.8 <sup>b</sup>
					Never	52	618 000	1.0	
					Ex	36	395 000	1.1	0.7–1.7 <sup>b</sup>
Tverdal et al. (1993)	Females 35–49	Norwegians in three areas	1972–78 to 1988 or emigrate	Age, area	1–24	22	287 000 <sup>b</sup>	0.9	0.5–1.5 <sup>b</sup>
					25+	14	117 000 <sup>†</sup>	1.4	0.7–2.6 <sup>b</sup>
					Never	7	157 431	1.0	
Tverdal et al. (1993)	Females 35–49	Norwegians in three areas	1972–78 to 1988 or emigrate	Age, area	Ex	4	38 953	2.3	0.5–9.1 <sup>b</sup>
					1–9	4	57 810	1.6	0.3–6.1 <sup>b</sup>
					10+	10	55 809	4.0	1.4–12.5 <sup>b</sup>

<sup>a</sup> C.I. are calculated 95% confidence intervals, when published C.I. are unavailable. Please see methods.

<sup>b</sup> Values were estimated from published data. Please see methods.

#### 4. Discussion

We found published, international, prospective associations between cigarette smoking and accident death in the US, UK, Norway, and Sweden (Table 1 and Fig. 1). The included associations are strongly positive in the heaviest smokers (RRs of 2.2–4 in four (Friberg et al., 1973; Tverdal et al., 1993; Doll et al., 1994) of the five populations with nine or more heaviest smoker deaths. The populations with heaviest smoker RR over 2 included 121 of 141 total heaviest smoker accident deaths (Table 1)). In doctors (Doll et al., 1994) and nurses (Kawachi et al., 1993) we were forced to use

injury minus suicide deaths as an approximation of accident death numbers, due to the lack of accident-specific published data in those populations. Six hundred thirty five accident deaths were studied in men but only 136 were studied in women. While accident deaths were significantly associated with smoking in Norwegian women, the summary association of accident death with smoking across all four female populations was  $RR = 1.36$  (95% CI 0.96–1.92,  $P < 0.1$ ). The lack of a significant summary association at the  $P < 0.05$  level in women may be due to lack of association or lack of statistical power (the low numbers of accident deaths studied may have reduced the statistical power of this

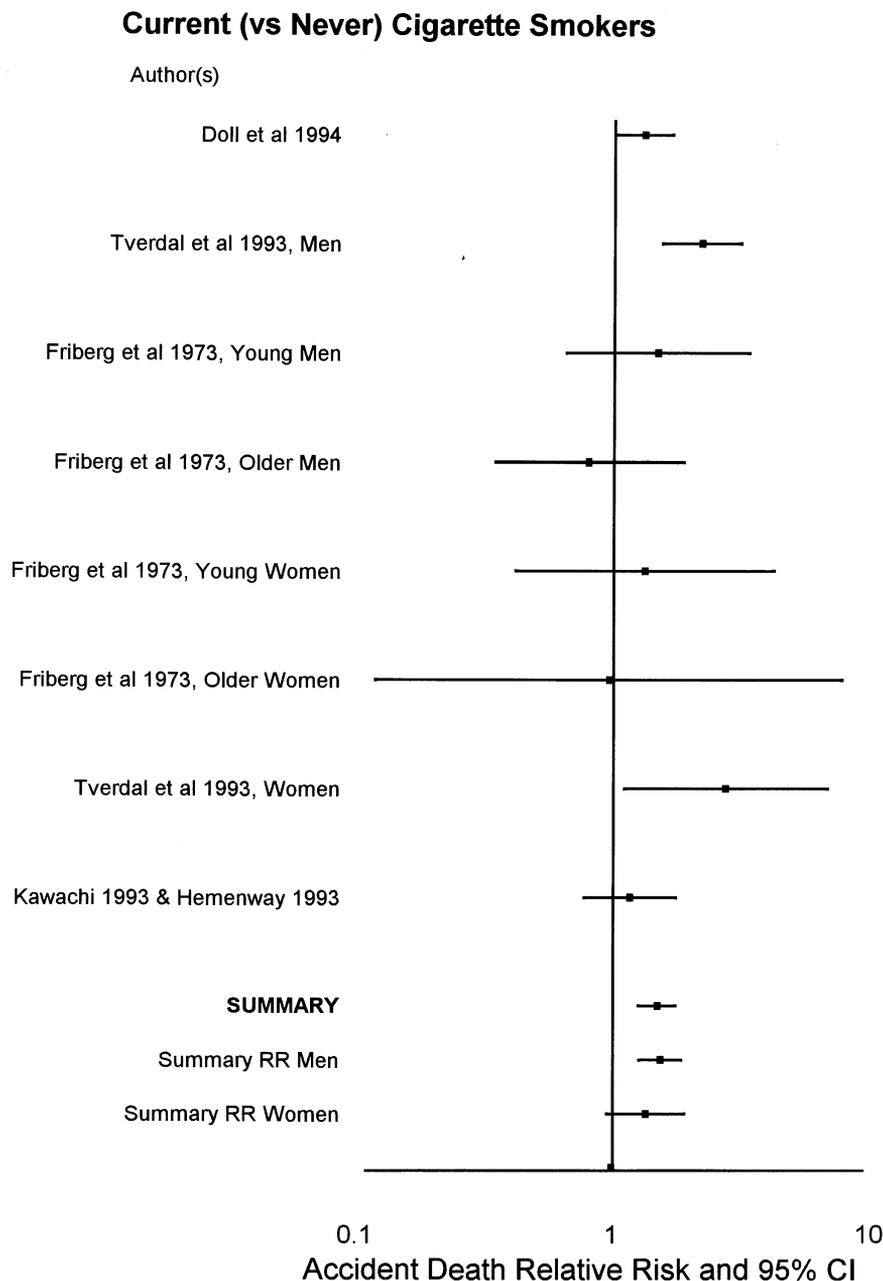


Fig. 1. Relative risks of accident death in current (versus never) cigarette smokers. The horizontal bars represent 95% confidence intervals.

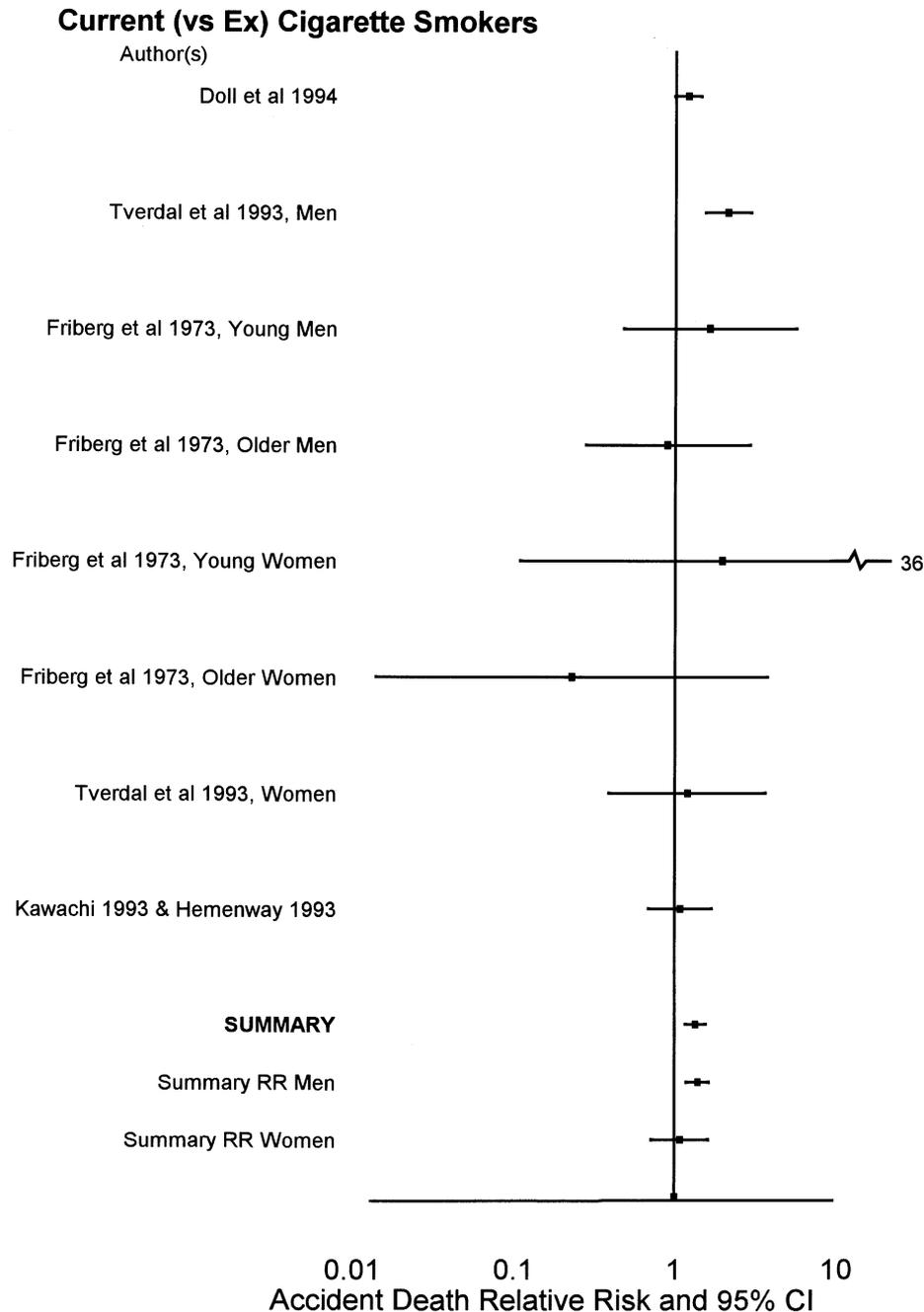


Fig. 2. Relative risks of accident death in current (versus ex smokers) cigarette smokers. The horizontal bars represent 95% confidence intervals. \* denotes value of the upper confidence limit, when the horizontal bar has been truncated.

study to detect a summary smoking/accident death association in women).

Similar, substantial, positive cohort associations between smoking and accidents are also present in all three additional populations that were excluded from quantitative summarization (they lacked incidence density data). Those populations include insured US veterans (Rogot and Murray, 1980), male Harvard or University of Pennsylvania entrants (Paffenbarger et al., 1969), and Southern California retirees (Ross et al.,

1990). Smoking was also associated with accidents: in postal workers (independent of drug use, job, exercise, and age) (Ryan et al., 1992); in elderly Greeks in a case-control study (Petridou et al., 1996); and in people with sleep disorders (Phillips and Danner, 1995). In a study published after our literature search, smoking is dose-response associated with violence (accident plus homicide) deaths in both the 500 000 men and the 600 000 women of the American Cancer Society's Cancer Prevention Study I (Burns et al., 1997). The associ-

ations appear to be based on valid measures of smoking, injury, and association. The associations were repeatedly shown in and biologically seem logically to be generalizable to at least middle-aged and older Americans and Northern Europeans and possibly to other humans. But the causes of much of the association are unclear.

Association often does not equal causation. Associations are more likely to represent causation when they are consistent, strong, dose-response, biologically plausible, and independent of other known causes.

Though possible, suggestions that the accident/smoking association might be non-causal, e.g. explained by familial (Kendler et al., 1993), personality (Doll et al., 1994), or alcohol use factors, or publication bias, are weakened by the above facts, other study types (see below), and these considerations. Most reported or estimated tests of associations between smoking and accident death had positive results. Exceptions were in populations lacking substantial numbers of accident deaths (Friberg et al., 1973). This argues against publication bias as an explanation for these results. A funnel plot (Egger et al., 1997) for Fig. 1 is not consistent with publication bias, though few points are available to plot. Associations between personality and smoking are described as 'very slight' (Dunn, 1974) and 'weak' (Patton et al., 1997). Smoking appears to contribute to feelings of anxiety, stress, and possibly negative affect (Department of Health, 1998), possible contributors to time-urgency and resultant accidents. The association between smoking and injury death is independent of alcohol use (Kawachi et al., 1993; Klatsky and Armstrong, 1993), as well as numerous other factors (Leistikow et al., 1998).

Cohort study evidence on whether smoking causes most smoking-associated accident deaths is limited by the low magnitude of the average smoker RR. There is a chance that additional adjustments for other possible factors such as familial factors (Kendler et al., 1993) and personality might make the smoking-accident association statistically insignificant. This possibility exists, but is diminished (Hill, 1965) by the consistency, dose-response (strong associations in heavier smokers), biological plausibility, and independence of the associations shown.

Information from forensic, toxicologic (challenge–rechallenge, in-vitro, and animal) cross-sectional, and randomized controlled human trials supports the cohort data suggesting that smoking may cause accident deaths. Cigarette smoking: (1) physically ignites fires and explosions; (2) biologically poisons and debilitates animals and humans; (3) may cause accidents through distraction/inattention; and (4) is associated with suggestive, but not statistically significant accident excesses in randomized controlled trial data.

(1) Smoking, or smoking and matches, causes up to 40% of residential or total fire deaths in North America, Europe, and Japan (Leistikow and Martin, 1999). Smoking continues to contribute to disastrous fires and explosions including, it is believed, the worst two single building industrial fire losses of life in modern history, the worst forest fire in world history, the worst industrial disaster in US history, and other disasters (Leistikow and Martin, 1999).

(2) The remarkable toxicities of tobacco and/or nicotine have led to their over 300 years of ongoing commercial use in poisoning various animals (Hayes and Laws, 1991; Farm Chemicals Handbook, 1997). Tobacco and/or nicotine also cause undesirable poisoning accidents in, at least, children, workers, and pets (Leistikow et al., 1998). Cigarettes account for about 15% of accidental poisonings of children in Greece (Petridou et al., 1995).

Perhaps more importantly, the smoking of tobacco and/or nicotine, and/or the withdrawals that result, cause physiologic performance decrements (Hirsch et al., 1985; Morton and Holmik, 1985; Perkins et al., 1989; Sandvik et al., 1995) that may reduce the smoker's ability to avoid or survive accidents. Smoking is associated with impaired performance on 'tests of muscle strength, agility and coordination, gait and balance, and self-reported functional status... after adjusting for age, ... activity, and alcohol use ( $P < 0.05$ )' (Nelson et al., 1994)

Smoking may increase the risk of serious complications (Warner et al., 1989; Forrest et al., 1992; Underwood and Bailey, 1993; Griep et al., 1996) and death (Dombi et al. 1995; Raff et al., 1996) from accidents that do occur. Smoking impairs the metabolic efficiency (Perkins et al., 1989) and fitness (Sandvik et al., 1995) that may be needed to survive the acute physiologic stress of accidents. Smoking (or nicotine) impairs the healing of diverse wounds in rats, hamsters, pigs and rabbits (Leistikow et al., 1998). Smoking (or perhaps nicotine) impairs human blood flow, tissue oxygenation, bone healing, and pulmonary toilet (Leistikow et al., 1998). Smoking may thus cause smokers' up to 10-fold excesses of wound infections (Kurz et al., 1996), traumatic skin and muscle sloughs, bone non-unions, and severe pulmonary complications following unconsciousness and trauma (Leistikow et al., 1998).

(3) Distractions or impairments in attention due to smoking may contribute to accidents. Nicotine withdrawal directly impairs attention (Heishman, 1998). The smoke, ashes, or burning embers of cigarettes may limit the vision or attention of smokers during dangerous tasks such as driving (Smoking caused 8000 vehicle fires in 1995 in the US [Hall, 1997]). Many smokers have had the distraction of coping with a burning cigarette or ember in their lap when one is dropped while driving [Leistikow, unpublished data].

(4) Randomized controlled trial data may be the ultimate way to quantify the impact of the myriad ways that smoking may contribute to accidents. Randomization to smoking cessation measures that maintained 30% absolute decrements in smoking prevalence during follow-up, is associated with substantial, albeit not statistically significant at the  $P < 0.05$  level, accident death reductions (RR = 0.62 [CI 0.26–1.50] in-trial and 0.7 [CI 0.40–1.22] including in-trial and post-trial follow-up) (Leistikow and Shipley, 1999).

This report has limitations. Cohort studies can show association, but can only suggest the possibility of causation. No Asian, South American, Southern European or African accident death studies were located. None of the populations included teenagers or young adults. Summary relative risk estimates are based on only eight populations. The ‘accidents’ analyzed in British doctors or US nurses possibly included some homicides. RRs from cohort studies are too high if not adjusted for confounders (extraneous factors misleadingly contributing to the association) and too low if adjusted for effects of the smoking. (such as smoking-caused risky behavior (Heishman, 1998; Parrott, 1998), and cerebral, cardiac, lung, cancer, ... disease) (Davey Smith et al., 1997). RRs from cohort studies are too low if explosions (Stephens, 1997) or other accidents from smoking injure non-smokers (e.g. 40% of those killed in one city’s cigarette fires were persons other than the initial smoker [Mierley and Baker, 1983]). The analysis addresses cigarette/accident associations. It provides little data on (a) associations between accidents and tobacco products other than cigarettes or (b) cigarette/accident sub-type associations.

In their 1969 annual Research Center presentation, the Philip Morris, Inc. Board of Directors was prominently told that smoking decreases the knee jerk reflex and that smokers exhibit excesses of accidents and injuries (Wakeham, 1969). The medical literature reviewed above increasingly allows physicians and the public access to studies supporting that recently released tobacco company document.

Disputes continue over the exact level of smoking (or other tobacco [Amoroso et al., 1996]) caused accident RRs in various populations, at various levels of tobacco, for various types of accidents. Even small smoking-caused excess accident death RRs have large global health implications. If baseline estimates of global disability adjusted life-years lost (DALYs) are correct (Murray and Lopez, 1997) and smoking causes adult only (age 15+) accident relative risks of 1.27–1.8, as seems plausible, then smoking-caused accident DALYs would represent 5–12% of accident DALYs; 0.6–1.5% of total global DALYs; or about 12–24% of all reported illness and injury DALYs from tobacco in the year 2000. In the year 2020, if male and female smoking rates are stable, these proportions would be 6–15% of

accident, 0.8–1.9% of total, and 8–18% of tobacco-caused burdens from illness and injury. The effects of cigar, pipe, chewing tobacco, increases in smoking (World Health Organisation, 1996a,b; World Health Organisation and the World Bank, 1996), youth smoking, or smoking-caused accident tolls in ex- or never-smokers (Aligne and Stoddard, 1997; Leistikow and Martin, 1999) are excluded from the above potential smoking-caused accident tolls.

Additional research is needed. Analyses of accident death RR in additional cohorts globally and twinships (especially smoking discordant mono- and dizygotic twinships) seem merited. Research prospectively assessing accident precursors and accidents as smoking begins and ceases in both observational and (smoking prevention or cessation) randomized controlled intervention trials also seems merited. Analyses should take care to exclude smoking-caused fire, explosion, and other accident deaths in nonsmoking ‘innocent bystanders’ from their never or never + ex-smoking reference group accident tolls in computing smoking-associated accident relative risks.

Smoking is a risk factor for accident deaths at least from fire, explosion, and poisoning. Some questions do remain about if, and exactly how, smoking is a risk factor for most other smoking-associated accident deaths. Yet numerous accident deaths are closely related to smoking, independent of at least age, race, and sex. Smoking seems to contribute to multiple accident and disease risks. Smoking cessation has numerous great benefits, including improved metabolic efficiency and stress test performance (Perkins et al., 1989). increased tissue perfusion (Sarin et al., 1974; Jensen et al., 1991), apparently reduced debility, distraction (Sacks and Nelson, 1994), distress (Parrott, 1995), and cortisol (Meliska et al., 1995) levels, and, possibly, reduced accident death rates (Multiple Risk Factor Intervention Trial Research Group, 1982; Kawachi et al., 1993; Amoroso et al., 1996) (Fig. 2).

Tobacco control is an accident control strategy practiced by some organizations (Tsai et al., 1992; Amoroso et al., 1996). It seems prudent to warn the general population, smokers, physicians, and policy makers of smoking’s associations with, and possibly large contributions to, accidental death.

### Acknowledgements

We wish to acknowledge the helpful comments of Ellen Gold and Steven Samuels and financial support from the Departments of Epidemiology and Preventive Medicine, Internal Medicine, and Employee Health, University of California, Davis.

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