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EPIDEMIOLOGY

Smoking as "independent" risk factor for suicide: illustration of an artifact from observational epidemiology?

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Two widely used criteria for determining whether an association between a risk factor and a disease is causal are dose response and independence from other factors. Data from a large US risk factor study (MRFIT) throw up a relation between cigarette smoking and suicide that meets these criteria, yet appears to be biologically implausible. It is likely that many more such associations, for other exposures and other diseases, are equally spurious, but are protected by their lack of obvious implausibility.

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Introduction

This paper has much in common with others appearing in general medical journals: it identifies yet one more "menace of daily life".¹ The paper is unusual, however, in that it discusses a finding which we do not think should be taken too seriously. On the other hand, we suggest that why such a finding was obtained, together with the reasons why we can dismiss it, are serious issues, which medical researchers and journal referees ignore at their peril.

Many reports in general medical journals concern the results of observational epidemiological studies. Data from planned observational studies or data collected for other purposes are analysed so as to relate outcomes—such as death from coronary heart disease or incident cases of breast cancer—to exposures which preceded the outcome. These exposures tend to be physiological or behavioural measures, such as serum cholesterol or leisure time physical activity. Exposures which are associated with the outcome of interest then become risk factors for that disease process. In this way, we have recently been told that lack of physical activity is a risk factor for diabetes,² that taking aspirin protects against colon cancer,³ that smoking could increase the risk of cervical cancer,⁴ and that low birthweight,⁵ not drinking alcohol,⁶ and poor dental health⁷ all predispose to coronary heart disease. Results such as these often receive considerable media attention, where they are presented as studies which have identified factors causally related to risk of disease. How are we to judge whether we are being led down another blind alley?

Researchers recognise that correlation does not imply causation: the risk factors may not cause (or prevent) the disease in question. These studies are, however, done in the hope of identifying causes. The effort to mount what are often huge enterprises would not be expended otherwise. While there are criteria, both internal and external to the data, which are traditionally invoked to help in the attribution of causality,⁸ two particular approaches to the data analysis itself are employed. One is to look for a dose-response relation between level of exposure (eg, amount of alcohol or physical activity and frequency of taking aspirin) and risk of the outcome. If such a relation is found it is taken to support a causal interpretation. The second strategy is to ascertain whether the association is "independent" of other risk factors. This is generally demonstrated by reporting the risk associated with the exposure of interest after statistically "controlling for" other risk factors. If the increase (or decrease) in risk remains significantly different from unity following adjustment, this is taken to increase suspicion of causality. To explore the robustness of these two methods we have applied them to an analysis of the risk of suicide associated with smoking in a large prospective cohort study.

Methods

In the MRFIT (Multiple Risk Factor Intervention Trial) study^{9,10} 361 662 men aged 35-57 were followed up for 12 years from screening. Baseline data include age, race, number of cigarettes currently smoked per day, whether participants were taking medication for diabetes (henceforth referred to as indicating diabetes), and whether participants had had a myocardial infarction. Socioeconomic status was indexed by matching the participant's postal zip code with data from the 1980 US census. Median family income for a zip code area is used as a marker of socioeconomic status, annual income under \$18 000 being classed as "low".

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TABLE I—SUICIDE RATES ACCORDING TO SMOKING BEHAVIOUR

| No of cigarettes smoked per day | No of men | No of suicides | Suicide rate per 10 000 person-years |
|---------------------------------|-----------|----------------|--------------------------------------|
| 0 | 228 545 | 291 | 1.09 |
| 1-19 | 29 333 | 50 | 1.47 |
| 20-39 | 72 200 | 166 | 2.00 |
| 40-59 | 27 844 | 78 | 2.46 |
| 60+ | 3740 | 16 | 3.78 |

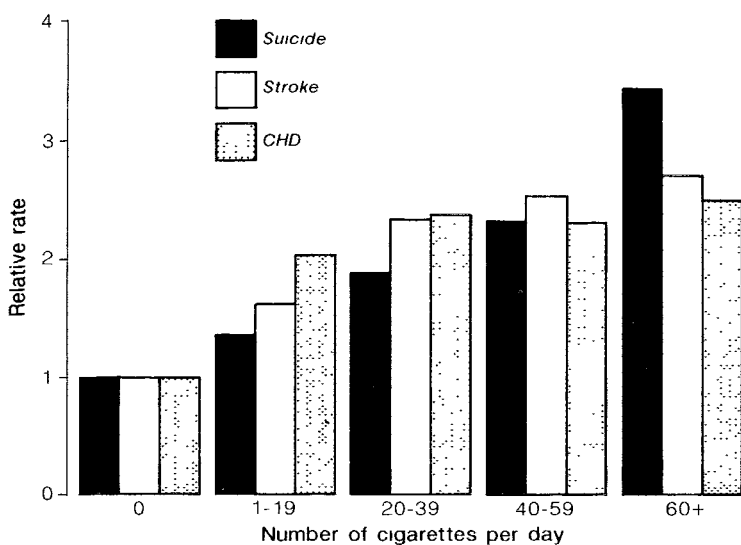
In our analysis death rates per 10 000 person-years of risk were calculated for groups defined according to reported smoking behaviour. The associations of smoking with death from suicide, homicide, coronary heart disease (CHD), and stroke are compared by stratified (by clinical centre) proportional hazards regression analysis.¹¹

Results

Over the 12-year follow-up there were 601 suicides. There is a clear dose-response relation between suicide risk and smoking (table I). Age-adjusted relative rates for death from CHD, stroke, or suicide, according to smoking behaviour, are presented in the figure.

Relative rates of suicide according to smoking behaviour, income, race, being diabetic, and having had a myocardial infarction are presented in table II. For income, there was an increased risk for participants living in low-income areas, but no trend outside this category, in line with findings from other investigations of the socioeconomic distribution of suicide.^{12,13} The suicide rate was lower in blacks, to the degree expected from US mortality data,¹⁴ although in our analysis this was not statistically significant. Participants who had the two severe illnesses on which data were gathered also had a raised risk of suicide, although this increase did not reach conventional levels of significance for diabetes ($p = 0.07$).

Prevalence of smoking was higher for participants living in low-income areas than for the rest (41.1% vs 34.6%, $p < 0.001$) so this factor would tend to accentuate an association between smoking and suicide. On the other hand, black men were more likely to be smokers (50.0% vs 35.9%, $p < 0.001$) and had somewhat lower rates of suicide, which could attenuate the association between smoking and suicide. Neither diabetes nor history of previous myocardial infarction were associated with smoking behaviour. When the relative rates of suicide according to smoking status are



Relative rates of death from suicide, stroke and coronary heart disease (CHD) according to smoking behaviour.

TABLE II—RELATIVE RATES OF SUICIDE (95% CI) ACCORDING TO RISK FACTORS

| Risk factor level | Age-adjusted relative rate | Fully adjusted relative rate |
|------------------------------|----------------------------|------------------------------|
| <i>Smoking</i> | | |
| 0 | 1.00 | 1.00 |
| 1-19 | 1.36 (1.00-1.83) | 1.36 (1.00-1.84) |
| 20-39 | 1.88 (1.55-2.27) | 1.86 (1.54-2.26) |
| 40-59 | 2.31 (1.79-2.96) | 2.27 (1.77-2.92) |
| 60+ | 3.44 (2.08-5.69) | 3.33 (2.01-5.52) |
| (χ^2 for trend) | (78.66, $p < 0.0001$) | (75.98, $p < 0.0001$) |
| <i>Income</i> | | |
| Low | 1.35 (1.13-1.60) | 1.33 (1.12-1.59) |
| Other | 1.00 | 1.00 |
| <i>Race</i> | | |
| Black | 0.85 (0.60-1.21) | 0.76 (0.53-1.08) |
| Other | 1.00 | 1.00 |
| <i>Myocardial infarction</i> | | |
| Previous | 1.79 (1.07-2.99) | 1.73 (1.03-2.90) |
| None | 1.00 | 1.00 |
| <i>Diabetes</i> | | |
| Diabetic | 1.66 (0.99-2.77) | 1.61 (0.96-2.70) |
| Not diabetic | 1.00 | 1.00 |

adjusted for these other risk factors there is little effect on the relative rates.

It may be argued that smoking is a plausible causal factor for suicide. The risk of being murdered has therefore also been analysed according to smoking status. As there are only 222 deaths due to homicide, smoking has been classified into three groups—no cigarettes, 1-39, and 40+. The relative rates (and 95% CI) of being murdered, adjusted for income and race which are both associated with risk of murder, are: 1.00, 1.71 (1.29-2.28), and 2.04 (1.32-3.15), respectively.

Discussion

Despite the replication of a previous finding^{15,16} it is improbable that cigarette smoking is a direct contributory cause of suicide. One could suggest that since smoking causes disease and since the suicide rate is higher in people who are ill, that smoking does have a causal role. However, the strength of the relation—roughly equivalent in magnitude to that between smoking and CHD—appears too strong to have arisen solely in this manner. A further suggestion might be that cigarette smoking may cause depression, although there is no good evidence, to our knowledge, for this. Alternatively, smoking and alcohol consumption are generally found to be related, the latter (not measured in this study) appearing to be associated with suicide risk in some studies.¹⁷ In a study which related both smoking and alcohol consumption to future suicide, smoking was a much stronger risk factor.¹⁶

Even if there is a remote possibility that the smoking/suicide relation could be causal or due to an obvious confounder, there can be no such suggestion for smoking/homicide. Given the lack of any plausible causative mechanism we are not misled by our result in this instance. We accept that the association is likely to have arisen because cigarette smoking is correlated with one or more factors predisposing to the mental state that increases the risk of suicide, not because it is itself a causal exposure.

It could be argued that the results presented here deserve little attention since the analyses were unplanned: the study was not established to explore whether smoking increased the risk of suicide and did not measure all potential confounders. Yet, despite apprehension regarding such analyses having been expressed for many years,¹⁸ they are common in epidemiology. Indeed it is perhaps unreasonable to expect researchers not to extend the boundaries of what they explore in data sets it has cost them dear to establish.

Even if these results can teach us little about suicide and homicide, they can teach us something about the inferences commonly made from epidemiological studies. The empirical evidence supporting the potential causal role of many "independent" risk factors is no stronger—indeed is often much weaker—than that presented here for cigarette smoking and death from suicide and homicide. On many criteria the findings reported here represent those which merit serious attention;¹⁹ the association is strong, has dose-response characteristics, and is apparently independent of confounding factors.²⁰ The principal difference between our example and the relations between cigarette smoking and cervical cancer^{21,22} or between weight at one year of age and plasma fibrinogen in adulthood^{23,24} is that the latter are not completely implausible.

The lack of plausible mechanisms to explain the smoking/suicide and smoking/homicide relationships is, however, the exception rather than the rule in epidemiology. For almost all of the associations which are demonstrated in epidemiological studies some "plausible biological mechanism" can usually be found. The finding that caffeine consumption is a risk factor for hip fracture, for example, could, it was suggested, be due to "the fact that caffeine increases urinary calcium losses and may produce a negative calcium balance".²⁵ Similarly, "changes in the quantity or quality of collagen or elastin" provide a possible mechanism to explain the epidemiological observation that cigarette smoking is an independent risk factor for premature skin wrinkling.²⁶

The apparent biological plausibility of a relationship in one direction often fails to preclude an equally plausible mechanism for a relationship in the opposite direction. When it was noted in a study of Kenyan prostitutes that oral contraceptive use was independently related to risk of future infection with the HIV²⁷ the authors could "hypothesise several potential mechanisms by which oral contraceptive use could facilitate HIV-1 acquisition". These included a direct effect on the genital mucosa, making it a less successful barrier to HIV, through to an immunosuppressive action which would increase susceptibility to HIV. When a recent study in Italians found the opposite, an independent and significant apparent protective effect of oral contraceptive use, a plausible mechanism was put forward to explain this too. This was that "progesterone-containing oral contraceptives thicken cervical mucus, which might be expected to hamper the entry of HIV into the uterine cavity". A hypothesis that an exposure causes a disease cannot be said to have been very strongly challenged by the requirement that it should be biologically plausible.

If epidemiology can throw up a spurious independent dose-response relation for smoking/suicide, how many more such relations, for other exposures and other diseases, are equally spurious, protected only by their lack of obvious implausibility? Look what happened with studies of risk factors for AIDS before the identification of HIV. In the United States, the use of amyl nitrite ("poppers") frequently accompanied unprotected anal intercourse.²⁹ Use of poppers could be easily quantified and was strongly correlated with the possibility of transmission of HIV. Poppers therefore emerged as an apparent independent risk factor for AIDS,³⁰ a theory which was generally dropped with the emergence of HIV as the widely accepted cause of AIDS.

The spurious nature of risk factors is generally less easy to demonstrate than it is for poppers and AIDS. Even when

the causal agents are included in studies, measurement imprecision leaves open the possibility that innocent exposures, which are correlated with these causes and can be more precisely measured, are incorrectly identified as risk factors.^{22,31} The degree to which this occurs is frequently underestimated and is difficult to quantify.^{32,33}

Smoking probably does not lead to suicide or being murdered—nor is it likely that owning the *Judy Garland Live at the Carnegie Hall* record causes AIDS.³⁴ However, it is likely that epidemiological studies would reliably identify these apparent menaces. There are 280 risk factors for CHD,³⁵ just as in 1882 there were numerous "causes" of typhoid fever;³⁶ and in 1856 *The Lancet* reported that smoking caused tottering knee, trembling hands, softening of the brain, cretinism, deafness, and spermatorrhoea.³⁷ Greater caution should be applied before dismissing the possibility that many of the risk factors currently being studied with great vigour are not artifacts of a similar type.

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HYPOTHESIS

Extraordinary unremitting endurance exercise and permanent injury to normal heart

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This hypothesis is that permanent cardiac injury could develop in some endurance athletes despite the absence of coronary atherosclerosis and ventricular hypertrophy. The proposed mechanism by which this injury could arise involves two physiological "vicious cycles". The first vicious cycle would occur between severe ischaemia and high catecholamines, the second would be between coronary vasospasm (induced by high catecholamines) and endothelial injury. The likelihood of the injury becoming permanent might increase if there is insufficient time between bouts of endurance exercise for regression of ischaemia and endothelial repair. Furthermore, magnesium ion deficiency, which can be induced by exercise, could exacerbate these vicious cycles and also contribute to catecholamine-induced thrombogenesis. In addition to ischaemia, there are several mechanisms, including the effect of free fatty acids liberated by the lipolytic effect of high catecholamines, that could cause direct myocardial injury.

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Introduction

Early man's survival before the development of even the crudest of weapons probably depended on his capacity for great endurance. This capacity is exemplified today by the Tarahumara Indians of northern Mexico who can chase a deer for up to 2 days until the animal drops from exhaustion.¹ Primitive hunting societies follow a "Palaeolithic rhythm" of 1 or 2 days of hunting, 6 to 8 h a day, followed by 1 or 2 days of rest.² Could some endurance athletes benefit by this restraint? In the past 2 decades there has been a sharp increase in the number of extremely challenging endurance events. Such events include the world's longest annual ultramarathon (over 1000 km) in Australia, and in the USA the most arduous yearly

marathon, to Pike's Peak (4300 m). The cavalier attitude to the potential cardiac risk may result partly from the popular belief promulgated by Karvonen and cited in a widely circulated textbook of the heart,³ that there is no evidence that strenuous athletic activity in a trained individual with a normal heart increases the risk of early death or morbidity from cardiovascular disease.

Morbidity related to endurance exercise

The case of a fatal myocardial infarction in the absence of significant coronary atherosclerosis reported by Green et al⁴ in a runner nearing the end of a marathon was complicated since the athlete probably also had heat stroke.⁵ Acute pulmonary oedema developed in 2 apparently healthy participants near the end of the 90 km Comrades Ultramarathon in South Africa. Follow-up studies revealed that the athletes' coronary arteries were angiographically normal and that there were no other apparent confounding factors.⁶ With regard to a permanent cardiac injury, Sy Mah, who set a world record of 524 marathons, was shown by stress tests to have probable exercise-induced coronary vasospasm with circadian variation 9 months before death from lymphoma at age 62 years. There was no history of heat stroke,^{4,5} nor were any other confounding factors found at necropsy, which revealed focal fibrosis of the left ventricular papillary muscles. It was postulated⁷ that these findings were related to exercise induced high concentrations of catecholamines.⁸

Two vicious cycles generating ischaemia and injury

The aetiology of coronary vasospasm is not fully understood. Only a 40–60% reduction in luminal diameter for 1 h is required to produce arterial endothelial damage and thrombosis.⁹ Coronary vasospasm secondary to

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