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Estimating the decline in excess risk of cerebrovascular disease following quitting smoking – A systematic review based on the negative exponential model

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ABSTRACT

We attempted to quantify the decline in stroke risk following quitting using the negative exponential model, with methodology previously employed for IHD. We identified 22 blocks of RRs (from 13 studies) comparing current smokers, former smokers (by time quit) and never smokers. Corresponding pseudo-numbers of cases and controls/at risk formed the data for model-fitting. We tried to estimate the half-life (*H*, time since quit when the excess risk becomes half that for a continuing smoker) for each block. The method failed to converge or produced very variable estimates of *H* in nine blocks with a current smoker RR <1.40. Rejecting these, and combining blocks by amount smoked in one study where problems arose in model-fitting, the final analyses used 11 blocks. Goodness-of-fit was adequate for each block, the combined estimate of *H* being 4.78(95%CI 2.17–10.50) years. However, considerable heterogeneity existed, unexplained by any factor studied, with the random-effects estimate 3.08(1.32–7.16). Sensitivity analyses allowing for reverse causation or differing assumed times for the final quitting period gave similar results. The estimates of *H* are similar for stroke and IHD, and the individual estimates similarly heterogeneous. Fitting the model is harder for stroke, due to its weaker association with smoking.

1. Introduction

In 1989, the US Surgeon-General concluded smoking causes stroke (US Surgeon General, 1989). The same year, a meta-analysis (Shinton and Beevers, 1989) concluded there was strong evidence of an excess risk, though varying by type of stroke, most evident for cerebral infarction and subarachnoid haemorrhage. The authors noted an excess risk of stroke in former smokers, but did not quantify how this declined by time quit. Some authorities subsequently made statements about this. The 1990 review of "The Health Benefits of Smoking Cessation" (US Surgeon General, 1990a) concluded that "After cessation, the excess risk decreases steadily. In some studies, the risk of stroke among former smokers becomes indistinguishable from that of never smokers within 5 years; in other studies, this decrease did not occur until after 10 years or more of smoking abstinence." More recently, the International Agency for Research on Cancer (IARC) Monograph "Reversal of risk after quitting smoking" (International Agency for Research on Cancer, 2007) examined the evidence in detail, noting that "Studies that have assessed the relationship of the duration of smoking abstinence on stroke risk report a marked risk reduction in 2–5 years after cessation, and the risk reduction continues up to 15 years after quitting. In some studies the risk declines to the level of never smokers within 5–10 years, but some studies report increased risk –though markedly lower than among continuous smokers – even after 15 years of abstinence." This review noted various methodological issues in assessing this evidence, including reverse causation, with some smokers quitting because of disease, and difficulties in accurately assessing smoking habits.

No one has previously attempted to quantify precisely the decline in excess stroke risk following quitting, using all available evidence and a formal model-fitting procedure. As in our earlier papers in this journal on the effects of smoking cessation on ischaemic heart disease (IHD) (Lee et al., 2012) and lung cancer (Fry et al., 2013), we use the negative exponential model to characterize the shape of the curve for each dataset by a single parameter. This parameter, the half-life (*H*), is the time since quitting when

Abbreviations: CI, confidence interval; DF, degrees of freedom; H, half-life; IARC, International Agency for Research on Cancer; IHD, ischaemic heart disease; REF, unique reference code for study; RR, relative risk; SE, standard error.

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the excess risk of a quitter reaches half that of a continuing smoker. Individual values of H can be used to assess between-study heterogeneity, and make overall estimates.

2. Methods

2.1. Inclusion and exclusion criteria

Attention was restricted to epidemiological prospective or case–control studies presenting data by time of quitting smoking on mortality or incidence of stroke (or types of stroke). The data had to be in a form allowing fitting of the negative exponential model, as described in Section 2.5 below. Studies of effects of quitting following a stroke were excluded, as were studies only presenting results for total cardiovascular disease, including IHD.

2.2. Literature searches

In April 2010, A PubMed search was conducted using the search terms "(stroke or cerebrovascular disease) and (quitting smoking or smoking cessation)", with abstracts inspected to identify possibly relevant publications. Additional relevant papers were sought from the IARC monograph on quitting (International Agency for Research on Cancer, 2007), the US Surgeon General report on quitting (US Surgeon General, 1990b), and papers identified in our similar review on IHD and quitting (Lee et al., 2012). In October 2011, an additional PubMed search was undertaken, using the search terms "(stroke or cerebrovascular disease or subarachnoid haemorrhage or intracerebral haemorrhage or cerebral infarction) and (quitting smoking or smoking cessation or former smoking or ex-smoking)". To avoid overlap with the previous search, this was limited to papers published since 1st January 2009. Finally, the April 2010 search was repeated, using the expanded search terms given above.

2.3. Identification of studies

Relevant papers were allocated to studies, accounting for multiple papers from the same study, and papers reporting on multiple studies. Each study was given a unique reference code (REF) of up to 6 characters, based on the name of the principal author or of the study. Care was taken to check whether different studies involved the same groups of subjects, thus avoiding double-counting in the meta-analyses. Where necessary, additional study details were obtained from other publications.

2.4. Data recorded

For each study, relevant information was entered onto a study database and a linked relative risk (RR) database. Note that, throughout this paper, we use the term RR to include its various estimators, including the odds ratio and hazard ratio. The study database contains a record per study containing data equivalent to those recorded for IHD (Lee et al., 2012). The data on the RR database relates to sequences of RRs ("blocks"). A block consists of a current smoker RR and a set of former smoker RRs by period of quitting, each RR being expressed relative to never smokers. Where originally expressed relative to current smokers, RRs were converted to be relative to never smokers, usually by the method of Hamling et al. (2008). The data recorded per RR were as described for IHD (Lee et al., 2012).

2.5. Statistical methods

The main features of the methods, described more fully previously (Lee et al., 2012), are summarized below.

2.5.1. Pseudo-numbers

We used the method of Hamling et al. (2008) to estimate the pseudo-table of the numbers of cases and the numbers either in the at risk population (for prospective studies) or of controls (for case–control studies) that correspond to the observed RRs and 95% confidence intervals (CIs). This forms the data for fitting the negative exponential distribution.

2.5.2. Estimated time quit

For each quitting period given in the source papers, we used the mid-point of the lower and upper times of quitting to estimate the time quit t_j to be used in the modelling. For the final, "open-ended above", quitting group we used the mean of the lower limit and either 50 years or the upper limit of the age range studied minus 20 years. t_j is taken as infinite for never smokers and zero for current smokers.

2.5.3. Fitting the negative exponential distribution to each block

For prospective studies, the underlying model, fitted to the data by maximum likelihood methods, is $P_j = A + B \exp(-Ct_j)$, where P_j is the absolute risk of disease at time t_j in group j, and A, B and C are parameters to be estimated. A is the risk in never smokers, A + B that in current smokers, and B the increase in risk for current smoking. H is estimated by $H = (\log_e 2)/C$. Goodness-of-fit to the model was assessed from the difference in log-likelihood between the fitted and the best-fit model.

For case–control studies, the model used is $F_j = 1 + B \exp(-Ct_j)$, where F_j is the RR (compared to never smokers) rather than the absolute risk. While C is interpreted as for prospective studies, B is not, being the excess relative rather than absolute risk.

2.5.4. Regression analyses

Sources of heterogeneity were studied by inverse-variance weighted regression of log H, between-block variation in log H being examined by study type, sex, continent, publication year, mean age of subjects studied, smoking product, current smoking RR, and numbers of cases in quitters.

2.5.5. Sensitivity analyses

Sensitivity analyses A and B investigated the dependence of H on possible "reverse causation". In A, the group with the shortest quitting time was omitted from each block. In B, all groups with an upper limit of quitting time <2 years were reallocated as current smokers. Sensitivity analyses C and D studied the effect of using time estimates for the final, open-ended, quitting group, based on algorithms alternative to that described in section the value of 50 years in that algorithm being replaced by either 30 years (C) or 70 years (S4).

2.5.6. Software

Data entry and most analyses were carried out using ROELEE version 3.1 (available from P.N. Lee Statistics and Computing Ltd., 17 Cedar Road, Sutton, Surrey SM2 5DA, UK), some analyses using Excel 2003.