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Using the negative exponential distribution to quantitatively review the evidence on how rapidly the excess risk of ischaemic heart disease declines following quitting smoking

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ABSTRACT

No previous review has formally modelled the decline in IHD risk following quitting smoking. From PubMed searches and other sources we identified 15 prospective and eight case-control studies that compared IHD risk in current smokers, never smokers, and quitters by time period of quit, some studies providing separate blocks of results by sex, age or amount smoked. For each of 41 independent blocks, we estimated, using the negative exponential model, the time, H, when the excess risk reduced to half that caused by smoking. Goodness-of-fit to the model was adequate for 35 blocks, others showing a non-monotonic pattern of decline following quitting, with a variable pattern of misfit. After omitting one block with a current smoker RR 1.0, the combined H estimate was 4.40 (95% CI 3.26–5.95) years. There was considerable heterogeneity, H being <2 years for 10 blocks and >10 years for 12. H increased ($p < 0.001$) with mean age at study start, but not clearly with other factors. Sensitivity analyses allowing for reverse causation, or varying assumed midpoint times for the final open-ended quitting period little affected goodness-of-fit of the combined estimate. The US Surgeon-General's view that excess risk approximately halves after a year's abstinence seems over-optimistic.

1. Introduction

It has long been known that smoking increases the risk of ischaemic heart disease (IHD), often referred to as coronary heart disease (CHD), and that the excess risk (i.e. the increase in relative risk (RR) compared to that in never smokers) declines on quitting smoking (US Surgeon General, 1979). However the time-pattern of decline in excess risk following quitting has never been precisely characterized, and statements made by authorities have varied. Thus, some years ago, the US Surgeon-General stated (1979) that "*cessation of smoking reduces the risk of mortality from coronary heart disease, and after 10 years off cigarettes this risk approaches that of the nonsmoker*", and 11 years later (1990) that "*the excess risk of CHD caused by smoking is reduced by about half after 1 year of smoking abstinence and then declines gradually. After 15 years of abstinence, the risk of CHD is similar to that of persons who have never smoked.*" More recently, in a Monograph "*Reversal of risk after quitting smoking*", the International Agency on Research and Cancer (IARC) (2007) examined the evidence in considerable detail, noting that "*Some studies find the risk to be similar to that in never smokers after 10–15 years abstinence, whereas others find a persistent increased risk of 10–20% even after 10–20 years.*" After noting a number of methodological issues in assessing this evidence, such as the problem of reverse causation with some smokers quitting because of disease and the difficulties in accurately assessing smoking habits, they pointed out that "*the body of evidence points toward the risk of CHD asymptotically approaching the risk of never smokers.*"

All the published assessments of the decline in excess risk are limited by being based on an impression gained from inspection of how the estimated RR, and its 95% confidence interval (CI), varies by time of quitting smoking, with no formal method used to fit curves to the declining pattern, or test whether patterns vary between studies. We attempt to rectify this omission by fitting, separately for each available data set satisfying certain defined criteria, a simple model to the observed decline. This model, the negative exponential, predicts that the risk asymptotically approaches the risk of never smokers, as suggested in the IARC Monograph (2007), and characterizes the shape of the curve by a single parameter which can be used to assess variation between studies. This parameter, the half-life (H), is the time at which the excess risk of a quitter reaches half that of a continuing smoker. While there are

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

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some limitations to our approach, which will be considered in the discussion, we believe that the analyses that we describe give some support for this model, and suggest its possible application to describing risk patterns following quitting for other smoking-related diseases, and perhaps also to describing risk patterns following other changes in smoking habits, such as reducing the amount smoked, or switching to a reduced exposure product.

2. Materials and methods

2.1. Inclusion and exclusion criteria

Attention was restricted to epidemiological prospective or case-control studies which presented data by time of quitting smoking on mortality or incidence of IHD, CHD, or acute myocardial infarction (AMI). The data had to be available in a form that allowed fitting of the negative exponential distribution, as described in the statistical methods below. Studies of effects of quitting following an AMI were excluded, as were studies which only presented results for total cardiovascular disease, including cerebrovascular disease.

2.2. Literature searches

In November 2009, relevant papers were sought from the Monograph on smoking cessation by IARC (2007), which was based on an extensive literature review. Additional papers were also sought from some earlier reviews of the epidemiology of heart disease and smoking (Lee, 2001; US Surgeon General, 1979, 1990, 2004), and from files on smoking and health accumulated over many years by P N Lee Statistics and Computing Ltd. A PubMed search was then carried out using the search terms "(quitting smoking OR former smoking OR ex smoking) AND (coronary heart disease OR ischaemic heart disease OR acute myocardial infarction)" to check for additional references in the previous three years. Papers were also sought from references cited in papers obtained. A further PubMed search was carried out in October 2011, also limited to the previous three years, but using the same search terms.

2.3. Identification of studies

Relevant papers were allocated to studies, taking into account 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, often based on the principal author's name, but sometimes based on the name of the study. Care was taken to try to avoid different allocated studies involving the same groups of subjects, which would lead to double-counting in the meta-analyses. However, limited overlap of subjects in different studies was allowed in some situations, where the alternative would have meant considerable loss of power. Where necessary, additional details of the studies were obtained from other publications describing them.

2.4. Data recorded

For each study, relevant information was entered onto a study database and a linked RR database. Note that, throughout this paper, the term RR is used to include its various estimators, including the odds ratio and the hazard ratio. The study database contains a record for each study describing the relevant publications, sexes considered, age range, populations and race(s) considered, location, timing, length of follow-up, study design, disease definition and fatality, types of controls, numbers of cases, and numbers either of controls or in the at risk population.

The data entered on the RR database relates to sequences of RRs ("blocks"). A block may consist of an RR for current smokers and a set of RRs for ex smokers by period of quitting, with each RR expressed relative to never smokers. Alternatively, it may consist of an RR for never smokers and a set of RRs for ex smokers by period of quitting, with each RR expressed relative to current smokers. The data recorded on the database for each RR included the block number, RR number within study, source reference details, sex, age range, race, smoking status (current, ex or never smoked, and for ex smokers the lower and upper times of quitting for each quitting period), product smoked (any product, cigarettes only, cigarettes +/− other products), comparison group (never or current smoker of any product, cigarettes or undefined), definition of disease, length of follow-up and adjustment variables, as well as the RR and its 95% CI and, for unadjusted data, the numbers of cases and controls in the numerator ("exposed group") and denominator ("unexposed group"). Also recorded was how the RR was derived (as given originally, from numbers, or taken from a graph) as well as whether the never smoking comparison group allowed for the inclusion of smokers of up to a minimum amount, as well as other information required for the statistical estimations to be carried out (as described in the next section).

Lower and upper times of quitting for successive quitting periods were recorded so that they ran on continuously. Thus, for example, an upper limit for a range given as 5–9 years, where the next range given had a lower limit of 10 years, was recorded as 10 years, as it was felt that the given range of 5–9 years included values of up to 9.999 years. Open-ended upper limits for the longest quitting period were entered as 999 years. Where the lower limit for the earliest quitting period was given as greater than 0 years, this value was entered directly. Thus, for an earliest period given as 1–5 years, it was assumed that quitters of less than 1 year had not been included. In many, but not all of these cases, the source papers had specifically noted that those who had quit for less than the lower limit had been excluded from analysis (or included among the current smokers). Values were entered as years, with values given as months converted to decimal years.

2.5. Statistical methods

2.5.1. Pseudo-numbers

The first step, for each block, was to use 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% CIs. Whether the RRs were originally expressed as relative to never smokers or relative to current smokers, the estimated pseudo-table consisted of a number of cases (n_j) and of controls or at risk (N_j) for never smokers, current smokers and quitters, by period of quitting. The subscript j is defined as 0 for never smokers, and runs from 1 to k for the quitting and current smoking groups. The estimation of the pseudo-table requires, in addition to the given RRs and 95% CIs, estimates of the proportion unexposed among the controls (or at risk) and of the ratio of total controls (or at risk) to total cases, as well as starting values for the number of unexposed cases and of controls (or at risk). These estimates had been entered on the database. The pseudo-table forms the data for fitting the negative exponential distribution.

2.5.2. Fitting the negative exponential distribution to data for prospective studies

The data fitted for each smoking group j in the block consists of the (pseudo-table) number of cases (n_j) and of at risk (N_j) together with an estimate of the time of quit (t_j). t_j is taken to be infinite for

never smokers, zero for current smokers, and an estimate of the midpoint time of the interval for ex smokers. Unless estimates of t_j were provided by the authors (in fact, never the case), the midpoint was estimated, for closed intervals, by the mean of the limits of the specified range of time quit. For intervals that were open-ended above, t_j was estimated as the mean of the lower limit and either 50 years or the upper limit of the age range studied minus 20 years, if this was smaller than 50 years. The value of 50 years is an approximate estimate based on data from older populations for those studies that give a detailed distribution of time of quit. However given that smokers are unlikely to start and quit smoking before age 20 years, the estimation also takes into account that assuming a 50 year upper limit might not be sensible for studies of younger populations.

The underlying model to be fitted to data from a block is of the form

$$P_j = \mathrm{A} + \mathrm{B}\exp(-\mathrm{Ct}_j) \quad (1)$$

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. Here A is the risk in never smokers, A + B is the risk in current smokers, and B is the increase in risk for current smoking. The term $\exp(-\mathrm{Ct}_j)$ models the proportional decline in excess risk for ex smokers, declining asymptotically from 1 to 0, as time increases. H is estimated by

$$0.5 = \exp(-CH) \quad (2)$$

or

$$H = (log_e 2)/C. \quad (3)$$

To estimate the parameters A, B and C, maximum likelihood methods were used. For each smoking group, the contribution to the log-likelihood function, L_j, (ignoring terms that do not vary in A, B or C) is given by

$$Q_j = \log L_j = n_j \log P_j + (N_j - n_j)\log(1 - P_j). \quad (4)$$

The overall log-likelihood for the block summed over the smoking groups, L, is then maximized using Newton–Raphson methods. For a sample of the data, these estimates were confirmed using Excel's solver routines based on the GRG2 algorithm (Lasdon et al., 1978) to maximize the likelihood. Formulae for the first and second derivatives of the log-likelihood with respect to A, B and C, and hence estimates of the variances of A, B, C and H, have been derived and are available on request. Goodness-of-fit to the model may be assessed by comparing the fitted value of L, with that for the maximum value possible ("best-fit model"), obtained by substituting $P_j = n_j/N_j$ in the formula for Q_j above.

2.5.3. Fitting the negative exponential distribution to data for case-control studies

The data fitted for each smoking group j in the block consists of the number of cases (n_j), the number of controls (N_j) and the times of quit (t_j), with the times of quit estimated as for prospective studies. Here, however, the model used is

$$F_j = 1 + \mathrm{B}\exp(-\mathrm{Ct}_j) \quad (5)$$

where F_j is the RR (compared to never smokers) rather than the absolute risk. Note that while C has the same interpretation as it has for prospective studies, the interpretation of B is different, being the excess RR rather than the absolute risk for prospective studies. Here there are more parameters to estimate. Apart from B and C, estimates are also required of $U_1, U_2 \ldots U_k$, the underlying frequencies in the controls for groups 1 to k, with the frequency for never smokers, U_0, being estimated so that the sum of the frequencies adds to 1. Based on the U_j, the relative frequencies of the cases are given by U_jF_j, so that the actual frequencies of cases are given by U_jF_j/z where

$$z = \sum_{j=0}^{k} U_j F_j \quad (6)$$

The contribution to the log-likelihood of group j is given (again ignoring terms that do not depend on the parameters) by

$$Q_j = \log L_j = N_j \log U_j + n_j \log(U_j F_j/z) \quad (7)$$

Again, the overall log-likelihood for the block, L, was maximized by Newton–Raphson methods, a sample of the estimates were confirmed using Excel, and formulae for estimation of the variance of B, C and H were derived. Here the likelihood of the best-fit model can be obtained by substituting the observed values of the RRs for F_j and the observed values of the frequencies of controls for U_j. Available on request as Additional file 1: Fitting are the formulae used for estimating the variance/covariance matrix of the log-likelihood functions with respect to the parameters A, B and C, and for deriving the standard error (SE) of H and of log H from these estimates. This file gives additional technical details on the procedures used for maximizing the log-likelihood function.

2.5.4. Regression analyses

Sources of heterogeneity were studied by inverse–variance weighted regression of log H. Between block variation in log H was examined by study type, sex, continent, publication year, mean age of the subjects studied, smoking category, smoking product, current smoking RR, and numbers of cases in quitters both one at a time, and using forward stepwise methods. The deviance of fitted models was used to indicate the extent to which the heterogeneity was explained. The estimates of log H and standard error of log H from the fixed effect models were then back transformed to give estimates of H together with 95% confidence limits. The regression analyses were restricted to studies of populations without specific diseases, the study of patients with human immunodeficiency virus (HIV) being reported separately.

2.5.5. Sensitivity analyses

Two alternative sensitivity analyses were conducted to study how dependent estimates of H were on possible "reverse causation". In the first of these analyses, RRs within a block which related to the earliest time of quitting were omitted. In the second, all RRs within a block which related to a time of quitting of up to 2 years were considered to be current smokers, with the pseudo-numbers for these RRs combined with those for the current smoking RR. These are referred to as sensitivity analyses A and B.

Sensitivity analyses were also conducted to study the effect of using alternative midpoint estimates for the final, open-ended above, quitting group. In the main analyses, the mean of the lower limit and either 50 years or the upper limit of the age range studied minus 20 years, if this was smaller than 50 years, was used. In the alternative algorithms the value of 50 years was replaced by either 30 years (sensitivity analysis C) or 70 years (sensitivity analysis D) in the calculation.

2.5.6. Software

All data entry and most statistical 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 were conducted using Excel 2003.

3. Results

3.1. Studies identified

Thirty-five publications satisfying the inclusion and exclusion criteria were identified from the searches carried out in November

Table 1
Literature searching; publications identified.

Source	Result
IARC review (2007)	16 Publications identified (Ben-Shlomo et al., 1994; Bosetti et al., 1999; Burns et al., 1997; Cederlöf et al., 1975; Cook et al., 1986; Dobson et al., 1991; Doll and Peto, 1976; Friedman et al., 1997; Hrubec and McLaughlin, 1997; Iso et al., 2005; Kawachi et al., 1994; Negri et al., 1994; Rosenberg et al., 1985; Rosenberg et al., 1990; US Surgeon General, 1990; Wen et al., 2005)
Lee review (2001)	7 new publications identified (Alderson et al., 1985; Alderson et al., 1986; Hammond and Horn, 1958; Hirayama and Wahrendorf, 1990; Paganini-Hill and Hsu, 1994; Tang et al., 1992; Tverdal et al., 1993)
US Surgeon General Reviews, 1979, 1990, 2004	3 new publications identified (Doll and Hill, 1964; Hammond and Garfinkel, 1969; Kahn, 1966)
Company smoking and health files	8 new publications identified (Baba et al., 2006; Doll and Hill, 1956; Garfinkel and Stellman, 1988; Kenfield et al., 2008; Rogot and Murray, 1980; Tavani et al., 2001; Taylor et al., 2002; Teo et al., 2006)
Medline search in Sept 2009 for last 3 years	279 hits 1 new publication identified (Honjo et al., 2010)
Medline search in Oct 2011 for last 3 years	278 hits 1 new publication identified (Petoumenos et al., 2011)

2009. As shown in Table 1, 16 of these were identified from the IARC review (2007) and only one from the first PubMed search, which produced 279 hits. One publication (Hammond and Horn, 1958), which reported results for coronary artery disease (CAD)

Table 2
Selected details of the 23 studies.

Study REF[a]/Main Ref. [b]	Location	Sex	Study type[c]	Start year(s)[d]	Follow-up years[e]	Outcome[f]	Fatality[g]	Comments[h]
ALDERS (Alderson et al., 1985)[i]	England	M + F	CCH	1977–82	–	IHD	NF	46 hospitals in 10 regions
BOSETT (Bosetti et al., 1999)[j]	Italy	F	CCH	1983–92	–	AMI	NF	Combined results from 2 studies[k]
BRHS (Tang et al., 1992)[l]	GB	M	P	1978–80	9	IHD	B	British Regional Heart Study
CEDERL (Cederlöf et al., 1975)	Sweden	M[m]	P	1963	9	IHD	F	Probability sample, national
CPSI (Hammond and Garfinkel, 1969)[n]	USA	M[m]	P	1959–60	6	CHD	F	ACS 25 state study
CPSII (US Surgeon General, 1990)[o]	USA	M + F	P	1982	12	CHD	F	ACS 50 state study
DOBSON (Dobson et al., 1991)	Australia	M + F	CCP	1988–89	–	IHD	B	WHO MONICA
DOLL (Doll and Peto, 1976)[p]	GB	M[m]	P	1951–52	20	IHD	F	Doctors
HAMMON (Hammond and Horn, 1958)	USA	M	P	1952	4	CAD	F	ACS 9 state study
HIRAYA (Hirayama and Wahrendorf, 1990)	Japan	M + F	P	1965	17	IHD	F	Six prefectures
HONJO (Honjo et al., 2010)[q]	Japan	M + F	P	1983–90	10	CHD	F	Pooled analysis of 3 studies
HRUBEC (Kahn, 1966)[r]	USA	M[s]	P	1954–57	26	CHD	F	War veterans
INTERH (Teo et al., 2006)	52 countries	M + F	CCH	1995–03	–	AMI	NF	INTERHEART
KAISER (Friedman et al., 1997)	USA	M + F	P	1979–86	6	CHD	F	Kaiser Permanente, California
NEGRI (Negri et al., 1994)	Italy	M + F	CCH	1988–89	–	AMI	NF	GISSI-2
NURSES (Kenfield et al., 2008)[t]	USA	F	P	1976–04	24	CHD	B	Nurses' Health Study
PAGANI (Paganini-Hill and Hsu, 1994)	USA	M + F	P	1981–85	10	CHD	F	Retirement Community in LA
ROSENF (Rosenberg et al., 1990)	USA	F	CCH	1985–88	–	AMI	NF	71 hospitals in 4 states
ROSENM (Rosenberg et al., 1985)	USA	M	CCH	1980–83	–	AMI	NF	78 hospitals in 4 states
TAVANI (Tavani et al., 2001)	Italy	M + F	CCH	1995–99	–	AMI	NF	Milan
TVERDA (Tverdal et al., 1993)	Norway	M[m]	P	1972–78	13	CHD	F	5 regions
WEN (Wen et al., 2005)	Taiwan	M	P	1989–92	11	IHD	F	Government employees, teachers
WHITEH (Ben-Shlomo et al., 1994)	England	M	P	1967–69	18	CHD	F	Civil servants

[a] Six character reference code used for study.
[b] Additional references giving results by time of quit are indicated against the specific studies.
[c] CCH = case-control study with hospital controls, CCP = case-control study with population controls, P = prospective study.
[d] Range of years when the case-control study was conducted or the baseline period for prospective studies.
[e] Only applicable to prospective studies. Relates to the longest period for which any publication reported results. In two studies the results used in analysis were for a shorter period – CPSI 6 years and HRUBEC 8 years.
[f] AMI = acute myocardial infarction, CAD = coronary artery disease, CHD = coronary heart disease, IHD = ischaemic heart disease.
[g] B = both fatal and non-fatal cases, F = fatal cases, NF = non-fatal cases.
[h] Abbreviations used: ACS = American Cancer Society, GISSI-2 = Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico-study 2, LA = Los Angeles, MONICA = Monitoring of Cardiovascular Disease.
[i] Additional reference (Alderson et al., 1986).
[j] Additional reference (Negri et al., 1994).
[k] Including study NEGRI.
[l] Additional reference (Cook et al., 1986).
[m] Study includes both sexes but the ex smoker results available for analysis are for men only.
[n] Additional reference (Burns et al., 1997).
[o] Additional references (Garfinkel and Stellman, 1988; Taylor et al., 2002).
[p] Additional references (Doll and Hill, 1956, 1964).
[q] Additional references (Baba et al., 2006; Iso et al., 2005).
[r] Additional references (Hrubec and McLaughlin, 1997; Rogot and Murray, 1980).
[s] Includes less than 0.5% women.
[t] Additional reference (Kawachi et al., 1994).

Table 3
Details of the 41 blocks used in analysis.

Block[a]	Study Ref.[b]	Sex	Age	Exposure[c]	Adjusted[d]	Current smoker RR	Cases in quitters[e]	Quitting groups (years)[f]
1	ALDERS	M	35–54	Cigarettes only	Age	1.79	67.8	⩽3, >3–10, >10[g]
2			55–74			0.73	97.8	
3		F	35–54			2.44	64.8	
4			55–74			1.67	113.8	
5	BOSETT	F	17–74	Cigarettes	Age + 10	4.10	23.1	1–<5, 5+[h]
6	BRHS	M	40–59	Cigarettes	Age + 2	2.13	90.7	1–2, 3–5, 6–10, 11–20, 21+
7	CEDERL	M	40–49	Any product	Age	2.40	9.7	<10, 10+
8			50–59			1.70	52.3	
9			60–69			1.40	125.6	
10	CPSI	M	40–79	Cigarettes only 1–19/day	Age	1.90	264.7	<1, 1–4, 5–9, 10–19, 20+
11				20+/day		2.55	559.9	
12	CPSII	M	30+	Cigarettes <21/day	Age	1.93	637.4	<1, 1–2, 3–5, 6–10, 11–15, 16+
13				21+/day		2.02	406.4	
14		F	30+	Cigarettes <20/day		1.76	120.9	
15				20+/day		2.27	101.3	
16	DOBSON	M	35–69	Cigarettes	Age + 1	2.71	224.4	<6 mo, 6–<12 mo, 1–3, 4–6, 7–9, 10–12,>12
17		F				4.70	49.8	
18	DOLL	M	30–54	Cigarettes only	Age	3.45	33.5	<5, 5–9, 10–14, 15+
19			55–64			1.69	134.8	
20			65+			1.30	312.1	
21	HAMMON	M	50–69	Cigarettes only <20/day	Age	1.75	157.1	<1, 1- < 10, 10+
22				20+/day		2.20	122.7	
23	HIRAYA	M	40+	Any product	Age	1.73	61.1	1–4, 5–9, 10+
24		F				1.90	2.2	
25	HONJO	M	40–79	Unspecified	Age + 1	2.22	251.1	<2, 2–4, 5–9, 10–14, 15+
26		F				2.86	25.7	
27	HRUBEC	M	55–64	Cigarettes	Age	1.67	920.3	1–4, 5–9, 10–14, 15+
28			65–74			1.54	1111.2	
29	INTERH	M+F	33–81	Any product	Age, sex + 5	3.04	1836.4	>1–3, >3–5, >5–10, >10–15, >15–20, >20[i]
30	KAISER	M	35+	Cigarettes only	Age	1.79	101.6	2–10, 11–20, >20[j]
31		F				1.79	36.7	
32	NEGRI	M + F	24–74	Any product	Age, sex + 7	2.90	146.1	1, 2–5, 6–10, 11+[h]
33	NURSES	F	30–55	Cigarettes	Age	3.33	383.8	<5, 5–<10, 10–<15, 15–<20, 20+
34	PAGANI	M	60–95	Cigarettes	Age	1.41	391.7	⩽5, 6–10, 11–20, >20
35		F				1.47	170.4	
36	ROSENF	F	25–64	Cigarettes	Age	3.60	142.0	1–3 mo, 4–6 mo, 7–11 mo, 1–<2, 2–<3, 3–5, 6–9, 10+
37	ROSENM	M	20–54	Cigarettes	Age	2.90	282.2	1–<2, 2–<3, 3–4, 5–9, 10–14, 15–19, 20+[i]
38	TAVANI	M + F	25–79	Any product	Age, sex + 10	2.20	96.5	1–4, 5–9, 10+[h]
39	TVERDA	M	35–49	Cigarettes	Age + 1	4.20	195.8	<3 mo, 3–12 mo, 1–5, 5+
40	WEN	M	35–64	Unspecified	Age	2.50	19.3	0–5, 6–16, 17+[k]
41	WHITEH	M	40–69	Cigarettes	Age + 1	1.74	338.2	1–9, 10–19, 20–29, 30+

[a] Where there is no entry in a column for a block, the value is that given in the next completed row above.

[b] The data are generally from the main reference shown in Table 2. However, exceptions are noted below, as are details of data not used in the analysis, with reasons for omission: ALDERS, The data from (Alderson et al., 1986) are the same as given in the main reference; BOSETT, Only the female data were used as the male data completely overlap NEGRI. There is some overlap of the female data with the data for NEGRI; BRHS, The data from (Cook et al., 1986) were not used as they were based on a shorter follow-up; CEDERL, The data for age group 40–69 years were omitted to avoid overlap; CPSI, The data used, from (Hammond and Garfinkel, 1969), are for 6 years follow-up. The data from (Burns et al., 1997), though for 12 years follow-up, were not used as they were adjusted for smoking duration; CPS II, The data from (Garfinkel and Stellman, 1988) were omitted as being virtually the same as given in the main reference. The data from (Taylor et al., 2002) were omitted as the detail was inadequate; DOLL, The data from (Doll and Hill, 1956, 1964) were not used as they were based on a shorter follow-up; HONJO, The data adjusted for smoking variables were not used. The data are combined results from three studies. To avoid overlap, data from the individual studies (Baba et al., 2006; Iso et al., 2005) were not used; HRUBEC, The data used, from (Kahn, 1966), are for 8 years follow-up. The data from this source for smokers of cigarettes only were not used as data for cigarettes are more commonly available in other studies. The data from (Hrubec and McLaughlin, 1997), though for 26 years follow-up were not used as there were no data for current smokers. The data from (Rogot and Murray, 1980), for 16 years follow-up, were not used as they were given graphically, and difficult to use; NEGRI, See BOSETT; NURSES, The multivariate data including adjustment for age of starting to smoke not used. The data from (Kawachi et al., 1994) were not used as they were based on shorter follow-up.

[c] "Cigarettes" = cigarettes ± other products (pipes and cigars), "Any product" = cigarettes and/or other products.

[d] Age + n (or Age, sex + n) indicates the number of other non smoking risk factors that were adjusted for: BOSETT, Education, study centre, cholesterol, diabetes, hypertension, hyperlipidaemia, family history of AMI, coffee, alcohol, body mass index (BMI); BRHS, Blood pressure, cholesterol; DOBSON, History of AMI or other IHD; HONJO, Cohort; INTERH, Region, exercise, fruit, vegetables, alcohol; NEGRI, Education, BMI, cholesterol, diabetes, hypertension, family history of AMI, coffee; TAVANI, Education, BMI, cholesterol, coffee, alcohol, physical activity, hyperlipidaemia, diabetes, hypertension, family history of AMI; TVERDA, Area; WHITEH, Employment grade.

[e] Estimated pseudo-numbers by method of Hamling et al. (2008).

[f] Based on time of interview for case-control and time of baseline interview for prospective studies, except that for prospective studies DOLL (blocks 18–20) and NURSES (block 33) time of quit was updated at intervals based on repeat interviews. Exceptionally, in studies HRUBEC (blocks 27 and 28) and WHITEH (block 41), and possibly also in study HONJO (blocks 25 and 26) the time of quit in subjects was recategorized during follow-up. Thus a subject reporting having quit for four years at baseline, would have been counted as having quit for nine years, five years later.
[g] Subjects were asked whether they smoked 1, 3, 5 or 10 years before hospital admission, or at ages 16, 20 and 25 years.
[h] Only quitters of at least one year were considered to be ex smokers.
[i] Quitters for less than a year were included among the current smokers.
[j] Only quitters of at least two years were considered to be ex smokers.
[k] Only quitters of at least six months were considered to be ex smokers.

was accepted as the definition appeared to be equivalent to that for IHD. The second PubMed search, in October 2011, produced 278 hits, but only two new relevant publications. One of these (Kondo et al., 2011) described results involving only three AMI cases in quitters, and was ignored. The other (Petoumenos et al., 2011) describes a study in HIV positive patients, and is considered separately.

The 35 publications identified in 2009 were divided into 23 studies. Table 2 gives selected details of these studies, including the study reference (REF), the main reference used as source for the data considered, and the additional references to data not actually used for reasons discussed below under "blocks rejected". Note that BOSETT and NEGRI have a small overlap inasmuch as they both include data for females interviewed in 1988–1989 in the GISSI-2 study. Note also that HONJO is based on a combined analysis of three studies. Results from two of these studies have been reported separately (Baba et al., 2006; Iso et al., 2005), but their data have not been included in our analyses, so as to avoid marked overlap.

Of the 23 studies, nine were conducted in the USA, nine in Europe, and three in Asia, with one in Australia and one conducted in 52 countries. The results relate only to males in ten studies, only to females in three, and to both sexes in ten. Fifteen were prospective studies, with follow-up periods ranging from 4 to 26 years, seven were case-control studies with hospital controls, and one was a case-control study with population controls. Of the eight case-control studies, six were of AMI and two of CHD, with only one including any fatal cases. Of the 15 prospective studies, all were of IHD, CHD or CAD, and only two included any nonfatal cases. Four of the studies started in the 1950s, three in the 1960s, five in the 1970s, nine in the 1980s and two in the 1990s. Although some studies related to specific populations, such as doctors, nurses or war veterans, none related to populations with specific medical conditions.

3.2. Blocks considered in the analysis

Table 3 gives some details of the 41 blocks considered in analysis. Of the 23 studies, 11 provided only a single block (five for males, three for females and three for sexes combined), five provided results only by sex, three only by age, and two only by level of consumption. One study provided blocks jointly by age and sex, and one jointly by sex and level of consumption. Seventeen of the blocks related to smoking of cigarettes, regardless of pipes and cigars, 13 to smoking of cigarettes only, eight to smoking of any product, and three to unspecified smoking. The RRs were adjusted for age in all 41 blocks, and for additional non-smoking variables (see footnote d of Table 3 for details) in 11 blocks, from nine studies. Numbers of cases in quitters (estimated from the pseudo-tables) ranged from less than 10 in block 7 (CEDERL, age 40–49 years) and block 24 (HIRAYA, females) to over 1000 in block 28 (HRUBEC, age 65–74 years) and block 29 (INTERH), with a median of 130.2. Current smoking RRs were, with one exception (block 2, ALDERS, males, age 55–74 years) above 1.0 in all blocks, exceeding 2.0 in 21 blocks, and 4.0 in three of these, the largest being the RR of 4.70 in block 17 (DOBSON, females).

Numbers of quitting groups ranged from two to eight, most commonly being three (12 blocks) or four (10 blocks). Generally quitting periods were as reported at time of interview in case-control studies, or as at baseline in prospective studies, with no updating of the time as follow-up progressed. However, in the prospective studies DOLL (blocks 18–20) and NURSES (block 33) time of quit was updated at intervals based on the latest information recorded in repeat interviews, with RRs related to the most recent quitting period reported. Also, time of quit was updated during follow-up in studies HRUBEC (blocks 27 and 28) and WHITEH (block 41), and may also have been updated in study HONJO (blocks 25 and 26). In most studies, length of time quit did not affect the definition of an ex smoker. However, quitters of less than a year were reclassified as current smokers in studies INTERH (block 29) and ROSENM (block 37). Also, WEN (block 40) excluded quitters of less than six months, BOSETT (block 5), NEGRI (block 32) and TAVANI (block 38) excluded quitters of less than a year, and KAISER (blocks 30 and 31) excluded quitters of less than two years, although none of these studies appeared to include the excluded ex smokers within the current smoking group.

3.3. Blocks rejected

As detailed further in footnote b to Table 3, some available data sets were not included in the main analysis. The reasons for this include avoidance of data from earlier follow-ups, when adequate data from a later follow-up were available, avoidance where possible of overlap between blocks, and avoidance of data sets where the only available RRs for quitters were relative to current smokers, and adjusted for other smoking variables, such as amount smoked, duration of smoking, or age of starting to smoke, since one cannot similarly adjust RRs for never smokers relative to current smokers. This last reason meant that, for study CPS I, data from a six year follow-up (Hammond and Garfinkel, 1969) rather than a 12 year follow-up (Burns et al., 1997) were used, and that, for study HRUBEC, data from an eight year follow-up (Kahn, 1966) rather than a 26 year follow-up (Hrubec and McLaughlin, 1997) were used.

3.4. Fitting the negative exponential model

Table 4 shows, for each of the 41 blocks, the data used for fitting the negative exponential model, including, for each smoking group, the complete set of RRs and CIs (expressed relative to never smokers), the pseudo-numbers of cases corresponding to these RRs ("cases observed"), and the value of the mean years quit assumed for each level of quitting. Table 4 also gives the results of fitting the negative exponential model to each of the blocks separately, showing the fitted RR values (again relative to never smokers), the fitted numbers of cases, the estimates of H and its SE, as well as the chi-squared value, χ^2(fit), degrees of freedom (DF), and the corresponding p value for goodness-of-fit. Available on request are two additional files. Additional file 2: Estimates gives further details of the fit, including the fitted values of the parameters A and B, and the full variance/covariance matrix of the estimates. Additional file 3: Plots presents a figure for each block, showing the goodness-of-fit of the negative exponential model.

Table 4
Fit of the negative exponential model to the data for the 41 blocks.

Block: study[a]	Sex[b]	Age[c]	Smoking group	Years quit	RR (95% CI)[d]	Fitted RR	Cases observed[e]	Cases fitted[f]
1: ALDERS	M	35–54	Current		1.79 (1.12–2.85)	1.99	95.96	99.51
			Ex	1.50	2.27 (1.25–4.10)	1.81	40.78	36.03
H = 5.18			Ex	6.50	1.21 (0.56–2.61)	1.42	14.33	15.37
SE(H) = 4.67			Ex	22.00	0.89 (0.41–1.92)	1.05	12.72	13.85
χ^2(fit) = 1.79	(6 DF)	p = 0.94	Never		1.00	1.00	43.16	42.20
2: ALDERS	M	55–74	Current		0.73 (0.44–1.20)	0.69	68.60	68.60
			Ex	1.50	1.31 (0.67–2.59)	1.00	29.74	27.07
H = 0.03			Ex	6.50	0.83 (0.40–1.73)	1.00	18.87	21.36
SE(H) = 728690			Ex	30.00	1.13 (0.64–2.00)	1.00	49.21	47.83
χ^2(fit) = 1.35	(6 DF)	p = 0.97	Never		1.00	1.00	51.86	53.43
3: ALDERS	F	35–54	Current		2.44 (1.67–3.57)	2.44	164.55	164.56
			Ex	1.50	2.05 (1.19–3.53)	2.05	40.51	40.50
H = 3.29			Ex	6.50	1.37 (0.66–2.81)	1.37	16.07	16.05
SE(H) = 2.76			Ex	22.00	1.00 (0.40–2.48)	1.01	8.26	8.32
χ^2(fit) = 0.0001	(6 DF)	p = 1.00	Never		1.00	1.00	68.71	68.65
4: ALDERS	F	55–74	Current		1.67 (1.17–2.37)	1.63	120.89	119.08
			Ex	1.50	1.22 (0.74–2.01)	1.44	38.14	41.11
H = 2.98			Ex	6.50	1.23 (0.75–2.03)	1.14	39.11	37.34
SE(H) = 4.85			Ex	30.00	0.92 (0.57–1.49)	1.00	36.53	38.09
χ^2(fit) = 0.83	(6 DF)	p = 0.99	Never		1.00	1.00	147.95	146.99
5: BOSETT	F	17–74	Current		4.10 (2.30–5.70)	3.99	64.90	64.23
H = 7.61			Ex	3.00	2.90 (1.30–6.70)	3.28	12.15	12.95
SE(H) = 6.16			Ex	27.50	1.30 (0.60–2.70)	1.24	10.91	10.60
χ^2(fit) = 0.13	(5 DF)	p = 1.00	Never		1.00	1.00	70.44	70.61
6: BRHS	M	40–59	Current		2.13 (1.59–2.86)	2.14	198.95	199.30
			Ex	2.00	1.80 (1.01–3.19)	1.74	13.53	13.01
			Ex	4.50	1.52 (0.90–2.56)	1.43	17.55	16.42
			Ex	8.50	0.98 (0.58–1.67)	1.18	17.44	20.90
H = 3.17			Ex	16.50	1.26 (0.80–1.97)	1.03	27.04	22.14
SE(H) = 1.99			Ex	30.00	0.84 (0.48–1.47)	1.00	15.14	18.01
χ^2(fit) = 2.31	(3 DF)	p = 0.51	Never		1.00	1.00	53.57	53.43
7: CEDERL	M	40–49	Current		2.40 (0.92–6.23)	2.70	25.99	28.88
H = 22.12			Ex	5.00	4.40 (1.49–13.04)	2.46	9.19	5.06
SE(H) = 42.05			Ex	19.50	0.53 (0.03–9.57)	1.92	0.51	1.82
χ^2(fit) = 4.40	(3 DF)	p = 0.22	Never		1.00	1.00	4.97	4.90
8: CEDERL	M	50–59	Current		1.70 (1.28–2.26)	1.78	212.05	215.68
H = 9.03			Ex	5.00	1.80 (1.19–2.73)	1.53	33.39	27.59
SE(H) = 5.90			Ex	24.50	0.90 (0.54–1.50)	1.12	18.94	22.85
χ^2(fit) = 2.05	(3 DF)	p = 0.56	Never		1.00	1.00	58.55	56.80
9: CEDERL	M	60–69	Current		1.40 (1.17–1.67)	1.40	348.61	348.24
H = 14.29			Ex	5.00	1.30 (0.98–1.73)	1.31	57.49	58.05
SE(H) = 13.98			Ex	29.50	1.10 (0.84–1.44)	1.10	68.15	67.88
χ^2(fit) = 0.01	(3 DF)	p = 1.00	Never		1.00	1.00	157.64	157.74
10: CPSI	M	40–79	Current		1.90 (1.76–2.05)	1.89	1011.95	1008.66
		(1–19/day)	Ex	0.50	1.62 (1.13–2.33)	1.74	29.13	31.47
			Ex	3.00	1.22 (0.94–1.58)	1.31	57.79	62.26
			Ex	7.50	1.26 (0.97–1.64)	1.06	56.44	47.83
H = 1.97			Ex	15.00	0.96 (0.73–1.26)	1.00	52.35	55.01
SE(H) = 1.15			Ex	35.00	1.08 (0.85–1.37)	1.00	68.96	64.11
χ^2(fit) = 2.54	(3 DF)	p = 0.47	Never		1.00	1.00	1781.91	1789.19
11: CPSI	M	40–79	Current		2.55 (2.41–2.70)	2.49	2971.01	2949.90
		(20+/day)	Ex	0.50	1.61 (1.25–2.07)	2.23	60.89	85.77
			Ex	3.00	1.51 (1.28–1.78)	1.47	149.11	147.83
			Ex	7.50	1.16 (0.98–1.38)	1.08	138.32	131.43
H = 1.81			Ex	15.00	1.25 (1.05–1.49)	1.00	131.71	107.60
SE(H) = 0.42			Ex	35.00	1.05 (0.84–1.31)	1.00	79.84	77.28
χ^2(fit) = 14.53	(3 DF)	p = 0.002	Never		1.00	1.00	1909.99	1941.10
12: CPSII	M	30+	Current		1.93 (1.74–2.14)	2.00	607.94	605.76
		(<21/day)	Ex	0.50	1.43 (0.84–2.42)	1.92	13.80	17.81
			Ex	2.00	1.61 (1.21–2.15)	1.71	48.59	49.70
			Ex	4.50	1.49 (1.11–2.00)	1.47	46.24	43.76
			Ex	8.50	1.28 (1.03–1.59)	1.24	89.23	82.89
H = 4.10			Ex	13.50	0.99 (0.80–1.23)	1.10	91.28	97.60
SE(H) = 1.01			Ex	33.00	0.88 (0.78–1.00)	1.00	348.27	381.54
χ^2(fit) = 6.45	(3 DF)	p = 0.09	Never		1.00	1.00	852.64	818.92
13: CPSII	M	30+	Current		2.02 (1.82–2.25)	2.00	575.88	573.98
		(21+/day)	Ex	0.50	2.56 (1.63–4.04)	1.95	18.85	14.45
			Ex	2.00	1.57 (1.11–2.22)	1.81	32.91	38.27
			Ex	4.50	1.41 (1.01–1.97)	1.63	35.58	41.37

(*continued on next page*)

Table 4 (*continued*)

Block: study[a]	Sex[b]	Age[c]	Smoking group	Years quit	RR (95% CI)[d]	Fitted RR	Cases observed[e]	Cases fitted[f]
			Ex	8.50	1.63 (1.27–2.09)	1.42	66.20	57.90
H = 6.71			Ex	13.50	1.16 (0.91–1.48)	1.25	69.96	75.81
SE(H) = 2.25			Ex	33.00	1.09 (0.93–1.28)	1.03	182.94	174.64
χ^2(fit) = 4.95	(3 DF)	p = 0.17	Never		1.00	1.00	817.09	823.00
14: CPSII	F	30+	Current		1.76 (1.33–2.33)	1.74	55.34	55.82
		(<20/day)	Ex	0.50	2.13 (0.68–6.64)	1.38	2.97	1.97
			Ex	2.00	0.87 (0.41–1.84)	1.05	6.93	8.54
			Ex	4.50	1.31 (0.72–2.39)	1.00	10.94	8.54
			Ex	8.50	0.74 (0.41–1.32)	1.00	11.55	15.93
H = 0.52			Ex	13.50	1.20 (0.73–1.96)	1.00	16.36	13.92
SE(H) = 0.74			Ex	33.00	1.17 (0.91–1.50)	1.00	72.20	62.99
χ^2(fit) = 4.60	(3 DF)	p = 0.20	Never		1.00	1.00	412.77	421.36
15: CPSII	F	30+	Current		2.27 (1.83–2.82)	2.18	106.38	106.32
		(20+/day)	Ex	0.50	1.41 (0.73–2.74)	1.38	8.99	9.15
			Ex	2.00	1.16 (0.62–2.18)	1.01	9.98	9.07
			Ex	4.50	0.96 (0.58–1.59)	1.00	15.76	17.10
			Ex	8.50	1.88 (1.24–2.86)	1.00	23.40	12.97
H = 0.30			Ex	13.50	1.37 (0.77–2.44)	1.00	11.92	9.06
SE(H) = 0.36			Ex	33.00	1.12 (0.78–1.62)	1.00	31.24	29.06
χ^2(fit) = 8.56	(3 DF)	p = 0.04	Never		1.00	1.00	358.21	373.15
16: DOBSON	M	35–69	Current		2.71 (2.07–3.53)	2.79	304.57	307.68
			Ex	0.25	4.31 (1.89–9.85)	2.66	20.47	17.28
			Ex	0.75	2.38 (0.91–6.20)	2.41	10.19	10.22
			Ex	2.50	1.95 (1.15–3.20)	1.81	36.18	34.80
			Ex	5.50	1.02 (0.60–1.74)	1.31	24.76	28.75
			Ex	8.50	1.40 (0.77–2.53)	1.12	21.83	19.08
H = 2.17			Ex	11.50	1.13 (0.67–1.89)	1.05	27.37	26.01
SE(H) = 1.01			Ex	31.00	0.96 (0.69–1.34)	1.00	83.60	85.59
χ^2(fit) = 3.50	(10 DF)	p = 0.97	Never		1.00	1.00	152.19	151.75
17: DOBSON	F	35–69	Current		4.70 (3.35–6.58)	4.86	112.17	112.35
			Ex	0.25	3.24 (1.15–9.19)	4.58	6.51	7.69
			Ex	0.75	9.97 (2.11–47.07)	4.08	5.40	3.71
			Ex	2.50	2.86 (1.23–6.66)	2.82	9.55	9.30
			Ex	5.50	1.29 (0.49–3.37)	1.74	5.63	6.87
			Ex	8.50	1.26 (0.49–3.21)	1.30	5.91	5.91
H = 2.30			Ex	11.50	1.71 (0.59–4.94)	1.12	4.95	3.51
SE(H) = 1.11			Ex	31.00	0.71 (0.37–1.35)	1.00	11.89	15.44
χ^2(fit) = 4.06	(10 DF)	p = 0.94	Never		1.00	1.00	112.76	109.99
18: DOLL	M	30–54	Current		3.45 (2.29–5.19)	3.04	73.02	72.91
			Ex	2.50	1.86 (0.83–4.19)	1.69	6.97	7.18
			Ex	7.50	1.21 (0.59–2.46)	1.08	9.76	9.91
H = 1.60			Ex	12.50	1.55 (0.76–3.16)	1.01	9.72	7.17
SE(H) = 1.47			Ex	24.50	1.62 (0.72–3.63)	1.00	7.08	4.95
χ^2(fit) = 2.19	(3 DF)	p = 0.53	Never		1.00	1.00	33.08	37.51
19: DOLL	M	55–64	Current		1.69 (1.32–2.18)	1.71	236.21	237.93
			Ex	2.50	1.88 (1.15–3.08)	1.66	18.78	16.55
			Ex	7.50	1.41 (0.95–2.09)	1.57	33.44	37.35
H = 24.43			Ex	12.50	1.73 (1.18–2.53)	1.50	37.59	32.52
SE(H) = 16.88			Ex	29.50	1.25 (0.87–1.80)	1.31	45.02	46.85
χ^2(fit) = 1.62	(3 DF)	p = 0.66	Never		1.00	1.00	78.73	78.57
20: DOLL	M	65+	Current		1.30 (1.09–1.55)	1.29	325.00	322.10
			Ex	2.50	0.99 (0.65–1.49)	1.26	23.92	30.54
			Ex	7.50	1.32 (1.02–1.72)	1.21	73.46	67.26
H = 17.41			Ex	12.50	1.13 (0.86–1.49)	1.17	62.27	64.72
SE(H) = 15.27			Ex	32.50	1.08 (0.88–1.33)	1.08	152.40	152.48
χ^2(fit) = 2.40	(3 DF)	p = 0.49	Never		1.00	1.00	186.93	186.88
21: HAMMON	M	50–69	Current		1.75 (1.59–1.92)	1.76	1072.45	1076.72
		(<20/day)	Ex	0.50	2.09 (1.38–3.16)	1.73	22.83	18.92
H = 10.42			Ex	5.50	1.54 (1.22–1.94)	1.53	78.61	77.84
SE(H) = 5.74			Ex	29.50	1.09 (0.83–1.43)	1.11	55.62	56.43
χ^2(fit) = 0.85	(3 DF)	p = 0.84	Never		1.00	1.00	714.59	714.19
22: HAMMON	M	50–69	Current		2.20 (1.97–2.45)	2.22	591.86	596.38
		(20+/day)	Ex	0.50	3.00 (1.89–4.77)	2.20	18.09	13.28
H = 29.08			Ex	5.50	2.06 (1.60–2.66)	2.07	64.22	64.44
SE(H) = 16.94			Ex	29.50	1.60 (1.17–2.20)	1.60	40.41	40.47
χ^2(fit) = 1.62	(3 DF)	p = 0.65	Never		1.00	1.00	697.33	697.32
23: HIRAYA	M	40+	Current		1.73 (1.52–1.97)	1.74	1740.60	1740.96
			Ex	3.00	1.50 (1.02–2.20)	1.60	28.38	30.20
H = 10.29			Ex	7.00	1.73 (1.10–2.72)	1.44	19.80	16.47
SE(H) = 8.21			Ex	30.00	0.94 (0.54–1.64)	1.10	12.93	15.05
χ^2(fit) = 1.08	(2 DF)	p = 0.78	Never		1.00	1.00	259.29	258.33

Table 4 (*continued*)

Block: study[a]	Sex[b]	Age[c]	Smoking group	Years quit	RR (95% CI)[d]	Fitted RR	Cases observed[e]	Cases fitted[f]
24: HIRAYA	F	40+	Current		1.90 (1.66–2.17)	1.90	259.10	259.10
			Ex	2.50	0.41 (0.05–3.37) [g]	–	–	–
H = 3.30			Ex	7.00	1.19 (0.20–6.94)	1.19	1.21	1.21
SE(H) = 11.70			Ex	30.00	0.91 (0.12–6.74)	1.00	0.94	1.03
χ^2(fit) = 0.01	(3 DF)	p = 1.00	Never		1.00	1.00	1131.46	1131.37
25: HONJO	M	40–79	Current		2.22 (1.82–2.71)	2.33	737.51	749.54
			Ex	1.00	1.62 (0.93–2.82)	2.26	14.09	19.02
			Ex	3.50	2.44 (1.78–3.35)	2.10	58.01	48.25
			Ex	7.50	2.36 (1.77–3.14)	1.88	79.93	61.87
H = 12.62			Ex	12.50	1.40 (0.98–2.01)	1.67	39.65	45.83
SE(H) = 3.41			Ex	32.50	1.04 (0.76–1.43)	1.22	59.45	67.50
χ^2(fit) = 10.33	(3 DF)	p = 0.02	Never		1.00	1.00	112.15	108.77
26: HONJO	F	40–79	Current		2.86 (2.25–3.62)	3.10	85.52	92.35
			Ex	1.00	5.11 (1.91–13.69)	2.95	3.96	2.28
			Ex	3.50	6.31 (3.46–11.53)	2.64	10.77	4.58
			Ex	7.50	2.63 (1.25–5.52)	2.24	7.09	6.01
H = 9.84			Ex	12.50	1.09 (0.26–4.45)	1.87	1.93	3.32
SE(H) = 5.45			Ex	32.50	0.60 (0.15–2.45)	1.21	1.95	3.94
χ^2(fit) = 10.01	(3 DF)	p = 0.02	Never		1.00	1.00	327.58	326.44
27: HRUBEC	M	55–64	Current		1.67 (1.56–1.78)	1.68	3100.09	3098.60
			Ex	3.00	1.35 (1.14–1.59)	1.51	156.66	173.84
			Ex	7.50	1.48 (1.30–1.69)	1.33	268.18	238.85
H = 7.28			Ex	12.50	1.13 (0.96–1.34)	1.21	155.00	163.55
SE(H) = 1.61			Ex	29.50	0.98 (0.87–1.11)	1.04	340.48	357.00
χ^2(fit) = 6.61	(3 DF)	p = 0.09	Never		1.00	1.00	1182.65	1171.20
28: HRUBEC	F	55–64	Current		1.54 (1.45–1.64)	1.53	2856.97	2841.20
			Ex	3.00	1.02 (0.78–1.32)	1.47	56.86	82.19
			Ex	7.50	1.37 (1.21–1.55)	1.39	309.43	313.66
H = 16.69			Ex	12.50	1.42 (1.24–1.61)	1.32	265.27	246.47
SE(H) = 4.17			Ex	29.50	1.12 (1.02–1.24)	1.14	479.63	485.55
χ^2(fit) = 10.51	(3 DF)	p = 0.01	Never		1.00	1.00	1540.22	1539.42
29: INTERH	M	33–81	Current		3.04 (2.85–3.25)	2.85	4338.79	4293.21
			Ex	2.00	1.87 (1.55–2.24)	2.38	238.99	272.30
			Ex	4.00	1.57 (1.25–1.97)	2.03	141.07	163.87
			Ex	7.50	1.51 (1.29–1.76)	1.61	311.64	329.80
			Ex	12.50	1.45 (1.25–1.69)	1.29	326.70	312.69
H = 4.71			Ex	17.50	1.55 (1.30–1.84)	1.14	247.64	211.70
SE(H) = 0.83			Ex	35.00	1.22 (1.09–1.37)	1.01	570.39	519.08
χ^2(fit) = 40.38	(9 DF)	p < 0.001	Never		1.00	1.00	2915.16	2987.74
30: KAISER	M	35+	Current		1.79 (1.39–2.31)	1.79	109.22	108.46
			Ex	6.50	1.30 (0.80–2.12)	1.47	18.42	20.71
H = 8.72			Ex	16.00	1.30 (0.91–1.85)	1.22	39.75	37.12
SE(H) = 5.58			Ex	35.50	1.00 (0.71–1.41)	1.05	43.46	45.25
χ^2(fit) = 0.53	(3 DF)	p = 0.91	Never		1.00	1.00	130.17	129.48
31: KAISER	F	35+	Current		1.79 (1.29–2.50)	1.78	57.63	57.21
			Ex	6.50	1.40 (0.71–2.75)	1.55	9.23	10.22
H = 12.72			Ex	16.00	1.40 (0.81–2.43)	1.33	14.82	14.08
SE(H) = 12.82			Ex	35.50	1.10 (0.61–1.98)	1.12	12.64	12.82
χ^2(fit) = 0.15	(3 DF)	p = 0.99	Never		1.00	1.00	89.50	89.49
32: NEGRI	M + F	24–74	Current		2.90 (2.20–3.90)	2.75	363.24	362.23
			Ex	1.50	1.60 (0.80–3.20)	1.89	15.81	17.79
			Ex	4.00	1.40 (0.90–2.10)	1.29	51.78	50.76
H = 1.55			Ex	8.50	1.20 (0.70–2.10)	1.04	24.44	22.95
SE(H) = 0.77			Ex	30.50	1.10 (0.80–1.80)	1.00	54.08	52.39
χ^2(fit) = 0.85	(7 DF)	p = 1.00	Never		1.00	1.00	98.37	101.61
33: NURSES	F	30–55	Current		3.33 (2.91–3.81)	3.37	525.98	522.80
			Ex	2.50	1.67 (1.31–2.12)	1.84	80.09	86.93
			Ex	7.50	1.23 (0.94–1.62)	1.11	58.77	51.74
			Ex	12.50	1.33 (1.01–1.75)	1.01	59.42	44.34
H = 1.67			Ex	17.50	1.20 (0.91–1.58)	1.00	58.77	48.16
SE(H) = 0.50			Ex	27.50	0.77 (0.63–0.94)	1.00	126.75	162.33
χ^2(fit) = 16.86	(3 DF)	p = 0.001	Never		1.00	1.00	358.94	352.41
34: PAGANI	M	60–95	Current		1.41 (1.03–1.93)	1.68	47.15	55.25
			Ex	3.00	2.02 (1.44–2.84)	1.56	38.61	29.34
			Ex	8.50	1.43 (1.02–1.99)	1.39	40.49	38.82
H = 10.75			Ex	16.00	1.21 (0.96–1.53)	1.24	106.35	107.50
SE(H) = 4.55			Ex	35.50	1.03 (0.85–1.25)	1.07	206.26	210.87
χ^2(fit) = 4.24	(3 DF)	p = 0.24	Never		1.00	1.00	200.72	197.81
35: PAGANI	F	60–95	Current		1.47 (1.10–1.95)	1.50	58.92	60.05
			Ex	3.00	1.28 (0.81–2.01)	1.46	20.15	22.93

(*continued on next page*)

Table 4 (*continued*)

Block: study[a]	Sex[b]	Age[c]	Smoking group	Years quit	RR (95% CI)[d]	Fitted RR	Cases observed[e]	Cases fitted[f]
			Ex	8.50	1.42 (0.93–2.15)	1.39	24.07	23.54
H = 23.92			Ex	16.00	1.53 (1.14–2.04)	1.32	56.53	48.47
SE(H) = 17.08			Ex	35.50	1.09 (0.83–1.42)	1.18	69.68	75.16
χ^2(fit) = 2.08	(3 DF)	p = 0.56	Never		1.00	1.00	220.74	219.96
36: ROSENF	F	25–64	Current		3.60 (3.00–4.40)	3.61	588.20	589.04
			Ex	0.167	3.00 (1.50–5.80)	3.29	13.97	14.79
			Ex	0.375	3.60 (1.80–7.20)	2.94	14.22	12.54
			Ex	0.75	2.30 (0.90–5.90)	2.45	6.43	6.70
			Ex	1.50	2.00 (1.10–3.70)	1.80	15.49	14.32
			Ex	2.50	1.30 (0.70–2.60)	1.36	11.83	12.28
			Ex	4.50	0.80 (0.40–1.80)	1.08	8.20	10.53
H = 0.88			Ex	8.00	1.10 (0.70–1.80)	1.00	23.53	21.80
SE(H) = 0.31			Ex	27.00	1.00 (0.70–1.40)	1.00	48.40	48.54
χ^2(fit) = 1.40	(11 DF)	p = 1.00	Never		1.00	1.00	177.96	177.83
37: ROSENM	M	25–64	Current		2.90 (2.40–3.40)	2.81	1365.48	1365.95
			Ex	1.50	2.00 (1.10–3.80)	1.55	18.00	15.72
			Ex	2.50	1.10 (0.60–1.90)	1.25	17.20	19.31
			Ex	4.00	1.00 (0.60–1.60)	1.08	23.89	25.87
			Ex	7.50	1.40 (1.10–2.00)	1.00	59.56	48.25
			Ex	12.50	1.00 (0.70–1.40)	1.00	54.05	55.43
H = 0.88			Ex	17.50	1.30 (0.90–1.80)	1.00	58.18	49.40
SE(H) = 0.41			Ex	27.00	0.80 (0.60–1.20)	1.00	51.29	62.40
χ^2(fit) = 9.55	(10 DF)	p = 0.48	Never		1.00	1.00	208.51	213.83
38: TAVANI	M + F	25–79	Current		2.20 (1.50–3.10)	2.56	149.30	150.22
			Ex	3.00	2.00 (0.90–4.00)	1.87	21.10	19.51
H = 3.54			Ex	7.50	1.10 (0.50–2.50)	1.36	12.74	13.25
SE(H) = 2.12			Ex	30.00	0.70 (0.50–1.10)	1.00	62.64	71.74
χ^2(fit) = 3.63	(6 DF)	p = 0.73	Never		1.00	1.00	126.89	117.95
39: TVERDA	M	35–49	Current		4.20 (3.37–5.23)	3.59	855.90	849.94
			Ex	0.125	3.83 (2.44–6.02)	3.41	23.92	24.72
			Ex	0.625	2.48 (1.58–3.90)	2.80	23.92	31.30
H = 1.18			Ex	3.00	1.77 (1.28–2.45)	1.44	62.32	59.05
SE(H) = 0.31			Ex	17.00	1.37 (1.02–1.85)	1.00	85.65	72.59
χ^2(fit) = 6.42	(3 DF)	p = 0.09	Never		1.00	1.00	87.60	101.70
40: WEN	M	35–64	Current		2.50 (1.54–4.06)	2.36	42.98	42.99
			Ex	3.25	1.55 (0.59–4.10)	1.45	4.79	4.77
H = 2.05			Ex	11.50	1.08 (0.46–2.50)	1.03	6.76	6.86
SE(H) = 2.67			Ex	30.50	1.35 (0.61–3.00)	1.00	7.80	6.13
χ^2(fit) = 0.51	(3 DF)	p = 0.92	Never		1.00	1.00	26.13	27.72
41: WHITEH	M	40–69	Current		1.74 (1.49–2.04)	1.68	768.40	767.23
			Ex	5.50	1.44 (1.03–2.03)	1.42	36.67	37.47
			Ex	15.00	1.19 (0.94–1.50)	1.19	103.06	106.29
H = 8.01			Ex	25.00	1.13 (0.89–1.43)	1.08	98.85	97.65
SE(H) = 4.27			Ex	39.50	1.15 (0.91–1.46)	1.02	99.67	91.74
χ^2(fit) = 1.10	(3 DF)	p = 0.78	Never		1.00	1.00	177.20	183.49
1–41: TOTAL			Current				27395.31	27340.93
			Ex	<2			517.07	535.63
			Ex	2–<5			1583.17	1683.61
			Ex	5–<10			2213.86	2124.71
			Ex	10–<15			1240.20	1208.80
			Ex	15–<20			982.36	881.88
			Ex	20+			3746.59	3805.24
			Never				18136.34	18234.13

[a] For each block, the block number and study reference code is shown. Also shown in this column is the estimate of half-life, H, its SE, SE(H), and the chisquared value for fit of the model, χ^2(fit), based on twice the difference in log-likelihood between the fitted model, and the best-fit model.

[b] Apart from the sex of the subjects considered in the block, the entries in the column also show the DF for χ^2(fit).

[c] Apart from the age group of the subjects considered in the block, the entries in the column also show the level of consumption (for blocks 10–15, 21–22 only) and the probability, p, value associated with χ^2(fit) and its DF.

[d] These estimates were as provided in the original source, except where it has been necessary to calculate them from adjusted rates (blocks 7–9, 21–22, 27–28, 39) or from adjusted observed/expected ratios (blocks 18–20), or to calculate 95% CI where only the RR was given (blocks 1–4). In some cases estimates were given in figures (blocks 6, 21–22, 36, 37). Where RRs and CIs were entered with a current smoker base (blocks 1–4, 18–20, 25–28, 33, 40) these have been recalculated with a never smoker base via the pseudo-numbers.

[e] These are pseudo-numbers of cases defined by the method of Hamling et al. (2008). Corresponding values for the controls and at risk population are available on request, as are the fitted values of the other parameters A and B.

[f] Corresponding values for the controls are available on request.

[g] RR not included in estimation as based on one death only.

Based on these results, some observations can be made. First, while there is in most cases no real indication of misfit, with the p value 0.05 or more in 34 of the 41 blocks, there are some blocks which deserve mention, considered in order of misfit. **Block 29** (INTERH, $p < 0.001$) – The RR declines rapidly initially up to 4 years quitting, but there is no evidence of further decline up to 17.5 years, and even after 35 years there is an excess RR compared to never smokers of 1.22 (95% CI 1.09–1.37). **Block 33** (NURSES,

$p = 0.001$) – The main source of misfit arises from the reduced RR at 27.50 years compared to never smokers of 0.77 (0.63–0.94). **Block 11** (CPS I, 20+/day, $p = 0.002$) – The main sources of misfit derive from the steep drop in RR up to 0.5 years, with a shallower decline later, and some evidence of a later rise between 7.5 and 15.0 years. **Block 28** (HRUBEC, females, $p = 0.01$) – Here the excess RR has virtually disappeared after 3 years, but reemerges, almost to the level of current smokers, after 7.5 and 12.5 years, before declining again. **Block 25** (HONJO, males, $p = 0.02$) – Little evidence of a decline is seen up to 7.5 years, after which the RR declines. **Block 26** (HONJO, females, $p = 0.02$) – Again there is no evidence of a decline up to 7.5 years, but here the RR in shorter-term quitters (1 and 3.5 years) is higher than in current smokers, though based on few cases. **Block 15** (CPS II, females, $p = 0.04$) – Here the RR declines steadily up to 4.5 years, by which time it is at about the level of never smokers. However, it rises again at 8.5 years, almost to the level of current smokers, before declining again. It is notable that in all the seven blocks mentioned the observed RRs do not show a monotonic pattern of decline with time quit, and the pattern of misfit is quite variable between the misfitting studies. Over all studies combined, the fit to the model seems quite reasonable.

It should also be noted that in block 2 (ALDERS, males, 55–74 years) the estimated SE of H, 728690, is very much larger than in any of the other blocks. This was the only block where the current smoker RR was less than 1. In subsequent analyses this block is ignored. As the statistical methods involve inverse–variance weighting, this block would in any case have had effectively zero weight.

3.5. Heterogeneity between estimates of half-life

It is clear that there is considerable heterogeneity between the estimates of H for the 40 blocks (omitting block 2). In 10 blocks the estimate is less than two years, while in 12 it is more than 10 years.

To investigate heterogeneity further, attention was restricted to those 33 blocks which showed no significant (at $p < 0.05$) evidence of misfit to their maximum likelihood fitted H value, with additional analyses carried out (results not shown), in which fixed H values of 1, 2, 4.40 (the weighted mean), 5, 10 and 20 years were fitted to each block. All seven of those blocks where the fitted H value was less than 2 years showed significant misfit to fixed values of 10 or 20 years, while six out of eight blocks where the fitted H value was more than 10 years showed significant misfit to fixed values of 1 or 2 years. In three of the remaining 18 blocks, with intermediate fitted H values, both high and low fixed H values

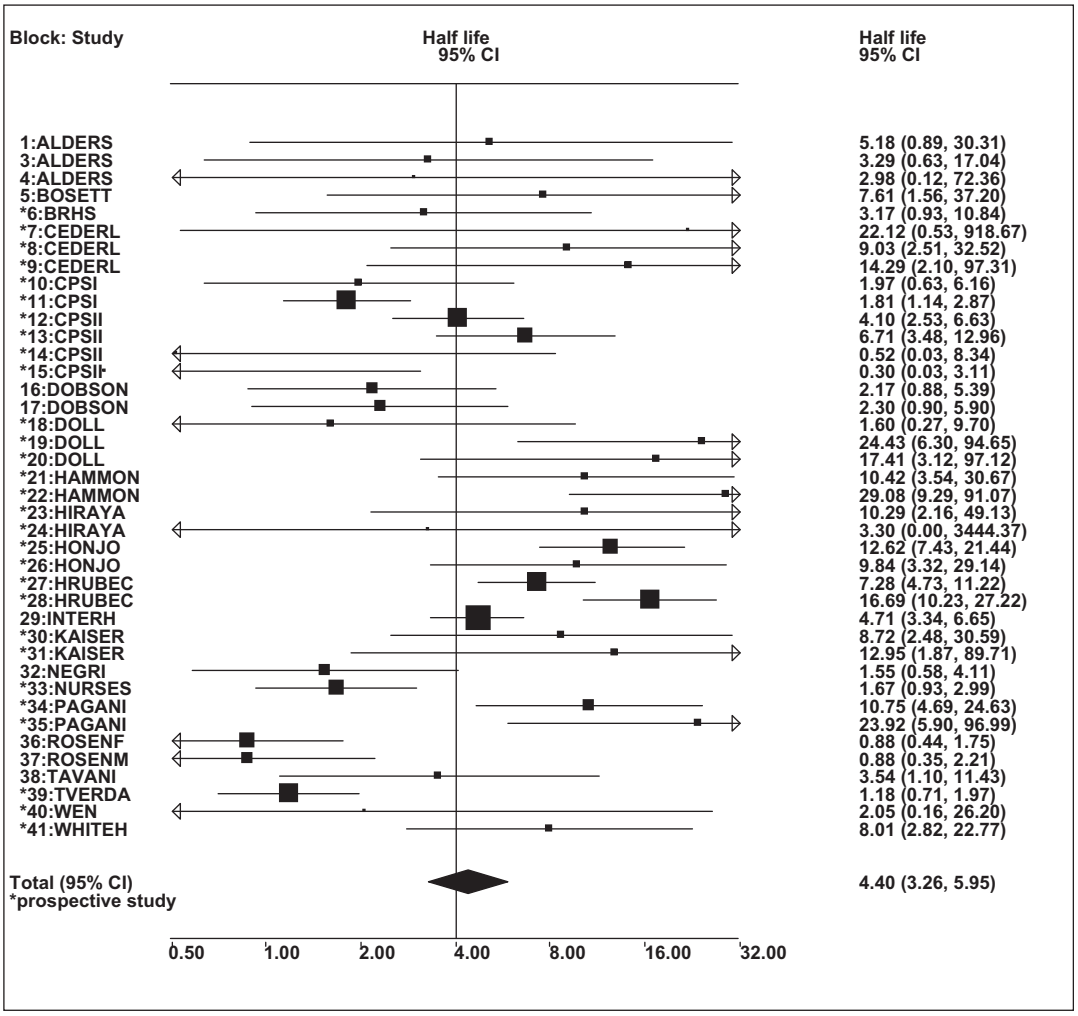

Fig. 1. Forest plot of half-life estimates. Tables 5 and 6 present results of inverse–variance weighted analysis of log H based on 40 blocks, with the estimates converted back to the original scale by taking exponentials. The individual study estimates and the 95% CI are shown in Fig. 1, both numerically, and graphically on a logarithmic scale. In the graphical representation individual RRs are indicated by a solid square, with the area of the square proportional to the weight (inverse–variance of log H). Arrows indicate where the CI extends outside the range indicated. Also shown is the combined estimate, based on inverse–variance weighted analysis of log H. This is represented by a diamond of standard height, with the width indicating the 95% CI.

Table 5
Weighted[a] estimates of H by various block characteristics.

Characteristic	Level	N[b]	p[c]	H (95% CI)
All	All	40	–	4.40 (3.26–5.95)
Study type	Case-control	11	0.06	2.84 (1.65–4.89)
	Prospective	29		5.26 (3.72–7.43)
Sex	Male	25	0.15	5.19 (3.62–7.43)
	Female	12		2.30 (1.08–4.87)
	Combined	3		4.12 (2.03–8.36)
Continent	North America	17	0.27	4.43 (2.97–6.60)
	Europe	15		3.05 (1.51–6.16)
	Asia	5		11.12 (4.03–31.06)
	Australia	2		2.23 (0.50–9.92)
	Multicountry	1		4.71 (2.15–10.32)
Publication year	Before 1990	12	0.12	6.40 (2.50–16.38)
	1990–1994	15		2.91 (1.76–4.79)
	From 1995	13		5.31 (3.59–7.86)
Age at start[d]	<50	12	<0.001	1.47 (0.91–2.39)
	50–59	14		5.22 (3.79–7.20)
	60–69	11		7.48 (4.56–12.28)
	70+	3		13.77 (4.28–44.35)
Smoking category	All	32	0.73	4.68 (3.29–6.65)
	Light[e]	4		4.08 (1.57–10.62)
	Heavy[f]	4		3.31 (1.44–7.62)
Smoking product	Cigarettes only	12	0.32	4.01 (1.94–8.30)
	Cigarettes[g]	17		3.91 (2.61–5.84)
	Any product[h]	8		4.61 (2.35–9.06)
	Unspecified	3		11.33 (3.85–33.31)
Current smoker RR	<1.50	4	0.004	13.83 (4.04–47.34)
	1.50–1.99	15		7.67 (4.90–12.00)
	2.00–2.99	14		3.89 (2.44–6.21)
	3.00–3.99	4		2.85 (1.68–4.85)
	4.00+	3		1.56 (0.66–3.67)
Cases in quitters	<100	14	0.27	4.76 (1.92–11.82)
	100–249	13		2.59 (1.35–4.98)
	250–499	8		4.98 (2.67–9.27)
	500–999	3		3.88 (2.13–7.07)
	1000+	2		7.16 (3.77–13.59)

[a] Based on inverse–variance weighted analysis of log H, with the estimates converted back to the original scale by taking exponentials.
[b] Number of blocks; block 2 is not included as the current smoker RR is less than 1.0 and the SE of H is extremely high.
[c] Probability value for difference between groups.
[d] Midpoint of age range (at baseline for prospective studies).
[e] Light = 1–19 or 1–20 cigarettes/day (see Table 4).
[f] Heavy = 20 + or 21 + cigarettes/day (see Table 4).
[g] Cigarettes regardless of pipe and cigar smoking.
[h] Smoked cigarettes, pipes and/or cigars.

failed to fit. For twelve of the 33 blocks considered in this analysis, the weighted mean H of 4.40 showed significant misfit.

It is clear from Table 4 that, over the 40 blocks, there is a strong relationship between the estimate of H and its SE. The mean SE is 0.64 for the 10 H values below 2.0, but rises to 3.00 for the 10 between 2 and 5 and to 4.49 for the eight between 5 and 10, reaching 13.42 for the 12 above 10. This suggests an approximate linear relationship between H and its SE, and that heterogeneity analysis would be better conducted based on estimates of log H.

Fig. 1 is a forest plot, giving the fitted H values and their 95% CI for each block individually and for the overall blocks combined. The data for the individual blocks are taken from the values returned from fitting the negative exponential model. The overall estimate of H of 4.41 (95% CI 3.25–5.96) is based on inverse–variance weighted regression analysis of log H, with the estimates back-transformed to the original scale. Table 5 shows the individual relationship of nine block characteristics to the fitted H. No significant (at $p < 0.05$) relationship was seen between H and study type, sex, continent, publication year, smoking category, smoking product or the number of cases in quitters, although the tendency for H to be higher for prospective than for case-control studies was close to significance ($p = 0.06$). The strongest relationship ($p < 0.001$) was the tendency for H to rise sharply with increasing age at start of the study. The only other characteristic significantly predictive of log H was the current smoker RR ($p = 0.004$), with H values clearly lower in blocks where the current smoker RR was high. It should be noted that current smoker RR and mean age at start are quite strongly negatively related, with the correlation coefficient −0.60 ($p < 0.001$).

Forward stepwise multiple regression analysis was also conducted. As shown in Table 6, the final model included mean age, smoking category, study type and publication year, but not current smoker RR. Estimates of log H increased with mean age. They were lower for the eight blocks (from studies CPSI, CPSII and HAMMON) where subjects were subdivided by amount smoked than for the other blocks, but there was no evidence that estimates differed between the four blocks for lighter smokers (<20 or <21 cigarettes/day) than for the heavier smokers (20 or 21+ cigarettes/day). Estimates were also higher for prospective than case-control studies, and for studies published before 1990. The deviance about the mean of 196.31 on 39 d.f. reduced to 49.26 on 31 d.f. in the full model.

3.6. Sensitivity analyses

Table 7 compares fitted H values and goodness-of-fit for the main and the four sensitivity analyses.

In sensitivity analysis A, where the RR for the earliest quitting period is removed from the block before fitting the negative exponential model, estimates of H are generally quite similar to those from the main model. However, there were two obvious exceptions. These related to block 7 (CEDERL, age 40–49 years) and block 8 (age CEDERL, 50–59 years), where removal of the RR for 1–9 years quitting left only one RR for quitting, which was below 1.0, so reducing the estimates from, respectively, 22.12 and 9.03 to 1.00. A similar situation pertained for block 24 (HIRAYA, females), although the reduction in the estimate was less, from 3.30 to 0.63. In block 14 (CPSI, females, <20 cigarettes/day), the five quitting RRs left in sensitivity analysis A were close to 1.0, with no evidence of a trend. In all these four blocks, the estimated SE of H (not shown) was extremely high. As referred to earlier, there were seven blocks in the main analysis where misfit occurred which was significant at $p < 0.05$. Five of these blocks remained significant misfits in sensitivity analysis A, but in block 11 (CPSI, 20+ cigarettes per day) and block 28 (HRUBEC, females) the misfit was no longer significant.

In sensitivity analysis B, RRs for quitting periods of up to 2 years are counted as relating to current smokers. This had no effect at all for 23 of the 40 blocks, where the earliest period of quitting extended up to more than 2 years, but meant the omission of between one and four RRs in the other 17 blocks. As is evident from Table 7, the estimates of H for these blocks are generally very similar to the corresponding estimate from the main analysis, the notable exception being block 15 (CPSII, females, 20+ cigarettes/day) where the estimate of H increased from 0.30 to 7.62.

In the main analysis the midpoint time of the final open-ended interval was estimated as the mean of the lower limit and either 50 years or the upper limit of the age-range studied minus 20 years, if this was smaller than 50 years. The value of 50 years in the above algorithm was replaced by 30 years in sensitivity analysis C, and by 70 years in sensitivity analysis D. In sensitivity analysis C the midpoint time was reduced in 38 blocks and unchanged in two, while in sensitivity analysis D the midpoint time was increased in 21 blocks and unchanged in 19. While there were some exceptions, the general effect was to decrease estimates of H slightly in sensitivity analysis C and increase them in sensitivity

Table 6
Fitted weighted regression model for log H.[a]

Characteristic	Level	Estimate (SE)	p[b]
Constant		0.805 (0.326)	0.019
Mean age[c]	<50	Base	
	50–59	1.467 (0.257)	<0.001
	60–69	2.088 (0.297)	<0.001
	70+	2.067 (0.474)	<0.001
Smoking category	All	Base	
	Light[d]	−1.093 (0.344)	0.003
	Heavy[e]	−1.094 (0.275)	0.003
Study type	Case-control	Base	
	Prospective	0.601 (0.213)	0.008
Publication year	Before 1990	Base	
	1990–1994	−0.997 (0.314)	0.003
	From 1995	−0.785 (0.311)	0.017

[a] Inverse–variance weighted. From forward stepwise procedure, successively introducing mean age ($p < 0.001$), smoking category ($p = 0.008$), study type ($p = 0.01$) and publication year (p = 0.01). The model allows the predicted H value for any block to be calculated by adding up the estimates corresponding to the block characteristics and then taking exponentials.
[b] For categorical characteristics, p values are relative to the base level.
[c] Midpoint of age range (at baseline for prospective studies).
[d] Light = 1–19 or 1–20 cigarettes/day (see Table 4).
[e] Heavy = 20 + or 21 + cigarettes/day (see Table 4).

analysis D. The largest proportional decreases in H in sensitivity analysis C were by 34% in block 5, by 29% in block 22, and by 27% in block 9, while the largest proportional increases in H in sensitivity analysis D were by 22% in block 20, and by 16% in blocks 23 and 35. Sensitivity analyses C and D had little effect on goodness-of-fit.

Overall weighted estimates of H based on the sensitivity analyses varied only between 4.35 and 4.81, quite similar to the estimate of 4.40 years for the main analysis.

3.7. Study of HIV positive subjects

Petoumenos et al. (2011) described the results of a multi-centre study conducted in Europe, Argentina, Australia and the USA involving 27,136 HIV patients enrolled from December 1999 and followed up to February 2008. Data on time of stopping or starting smoking was not recorded, but patients reporting being a current smoker on one visit and being a nonsmoker at the next were taken to have quit halfway between the two visit times. Similarly patients restarting smoking were considered current smokers from halfway between the relevant visits. The authors compared risk of AMI (fatal and nonfatal) in never smokers, current smokers, and quitters during follow-up by quit period, adjusted for cohort, calendar year, age, sex and various indicators of cardiovascular risk and HIV treatment. Converting these estimates to be relative to never smokers using the method of Hamling et al. (2008) gives RR (95% CI) estimates of 3.45 (2.59–4.59) for current smokers, and of 3.79 (2.47–5.84), 3.03 (1.83–5.03), 2.66 (1.42–4.96) and 2.10 (1.18–3.75) for quitters during follow-up of <1, 1–2, 2–3 and >3 years, respectively, based on a pseudo-number of 78.7 cases in quitters. Using time midpoints of 0.5, 1.5, 2.5 and 4.5 years, H was then estimated as 4.30 (SE 2.35) years, with no evidence of misfit. This is close to the weighted mean of 4.40 years for the main analyses. A quite similar estimate of 5.81 (SE 4.16) years was obtained based on additional results provided by the authors for an endpoint including CHD treated by an invasive coronary procedure in addition to AMI, an endpoint which is somewhat different from any used in the other studies.

4. Discussion

4.1. Advantages of the negative exponential model

Although not derived from theoretical considerations, the negative exponential model has a number of attractions. It has a simple functional form, allowing the curve of the decline in excess risk by time of quit to be quantified by a single parameter, H, with an easily understood interpretation. Thus, if the RR from current smoking is 3 so that the excess risk is $3 - 1 = 2$, and H is estimated as 5 years, one can readily see that the RR will be $1 + 0.5 \times 2 = 2$ after 5 years, $1 + 0.5 \times 0.5 \times 2 = 1.5$ after 10 years, $1 + 0.5 \times 0.5 \times 0.5 \times 2 = 1.25$ after 15 years, and so on asymptotically towards 1.0. Having an estimate of H and its SE also allows derivation of inverse–variance weighted combined estimates for a set of data blocks, and comparison of estimates by block characteristics such as sex, age or study type. Provided the model fits the observed data reasonably well, use of the negative exponential model should be a useful tool for summarizing data in a meaningful way. As far as we are aware, no one has previously attempted to use this or other models to try to summarize the evidence on the decline in excess risk following quitting.

4.2. Fit to the negative exponential model

We fitted the model separately for 41 data blocks, and found that generally it did fit the observed data well. It is perhaps unsurprising that the model should fit data adequately for blocks which are based on a limited number of time periods and relatively few IHD cases in quitters, and where the RRs decline monotonically with increasing time of quitting. However, as is evident from Table 4, it also fits data from a number of blocks which are based on five or more time periods and quite a substantial number of quitters, and where there are some fluctuations in the RRs as quitting time increases. There are, as described in the results section, seven blocks where a statistically significant misfit was seen, but these seem to be more a result of unusual patterns in the data, which vary from study to study, rather than any general deficiency of the model. Thus for example, the pattern of a lack of decline in RR between about 4 and 17.5 years quit seen in block 29 (INTERH) clearly differs from that seen in most other blocks, while the significant reduction in risk in long-term quitters compared to never smokers in block 33 (NURSES) is also not generally evident elsewhere. Even where the model does not fit precisely, it still clearly explains a very large part of the variation in RR by time of quit.

4.3. Heterogeneity between estimates

While we feel that deriving an estimate of H using the negative exponential model is in general a valid and useful way of data summary, one should bear in mind the clear evidence of heterogeneity between estimates from different data blocks. Our overall estimate of H of 4.40 (95% CI 3.26–5.95) years, based on 40 blocks (ignoring block 2 where the RR for current smokers compared to never smokers was less than 1.0) is clearly inconsistent with the data for a number of blocks with lower or higher H estimates. Nor is it consistent with the statement by the US Surgeon-General (1990) that "the excess risk of CHD caused by smoking is reduced by about half after 1 year of smoking abstinence", as an H of 1.0 significantly ($p < 0.05$) misfits the data from almost half the blocks studied, with the misfit highly significant ($p < 0.001$) in about a quarter. The heterogeneity we observed is more consistent with the statement made in the IARC Monograph (2007) "Some studies find the risk to be similar to that in never smokers after 10–15 years abstinence, whereas others find a persistent increased risk

Table 7
Comparison of fitted H values and goodness-of-fit for the main and sensitivity analyses.[a]

Block[b]	Main analysis[c]	Sensitivity analysis A[d]	Sensitivity analysis B[e]	Sensitivity analysis C[f]	Sensitivity analysis D[g]
1	5.18	3.44	–	5.01	–
3	3.29	3.28	–	3.28	–
4	2.98	4.26	–	2.75	3.00
5	7.61	8.16	–	5.02	8.16
6	3.17	3.04	3.11	3.13	–
7	22.12	[1.00]	–	–	–
8	9.03	[1.00]	-	8.04	–
9	14.29	[14.75]	–	10.40	–
10	1.97	2.08	2.10	1.98	1.97
11	1.81**	2.03	2.07	1.81**	1.81**
12	4.10	4.10	4.24	3.70	4.24
13	6.71	6.76	7.11	6.37	6.40
14	0.52	0.03	1.70	0.52	0.52
15	0.30*	0.56*	7.62	0.30*	0.30*
16	2.17	2.18	2.12	2.16	–
17	2.30	2.29	2.20	2.25	–
18	1.60	2.20	–	1.61	–
19	24.43	24.56	–	20.73	–
20	17.41	17.31	–	13.57	21.32
21	10.42	10.35	10.25	8.27	–
22	29.08	29.59	28.78	20.78	–
23	10.29	11.25	–	8.43	11.94
24	3.30	[0.63]	–	3.12	3.34
25	12.62*	12.60*	12.76*	10.61**	13.44*
26	9.84*	9.79*	9.61*	8.58*	10.36*
27	7.28	7.76	–	6.63*	–
28	16.69*	17.16	–	13.17**	17.39*
29	4.71***	5.24***	–	5.34***	4.54***
30	8.72	9.74	–	7.60	9.27
31	12.95	14.04	–	11.16	14.28
32	1.55	1.76	1.83	1.55	1.55
33	1.67***	3.20**	–	1.67***	–
34	10.75	12.41	–	9.08	11.88
35	23.92	22.19	–	20.55	27.71
36	0.88	0.89	0.71	0.88	–
37	0.88	0.48	0.48	0.88	–
38	3.54	2.74	–	2.92	3.73
39	1.18	1.18	1.33	–	–
40	2.05	1.66	–	2.07	–
41	8.01	8.27	–	8.78	–
Total[h]	4.40	4.79	4.81	4.43	4.35

[a] The values shown in the table are the fitted H values. Where there is evidence of misfit, this is indicated by: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
[b] See Table 3 for details of the blocks. Block 2 is omitted as the current smoker RR was less than 1.0.
[c] Results as shown also in Table 4.
[d] Omitting the estimate in each block with the lowest quitting period. Estimates in square brackets are those for blocks where this omission left only a single RR for quitters.
[e] Counting estimates with an upper limit of quitting time up to 2 years as applying to current smokers. Dashes indicate where this did not affect the data considered.
[f] Midpoint time for the final, open-ended, period of quitting which is estimated as the mean of the lower limit and either 30 years or the upper limit of the age range studied minus 30 years, if this is smaller than 30 years. Dashes indicate where this did not affect the data considered.
[g] Midpoint time for the final, open-ended, period of quitting which is estimated as the mean of the lower limit and either 70 years or the upper limit of the age range studied minus 70 years, if this is smaller than 70 years. Dashes indicate where this did not affect the data considered.
[h] The inverse–variance weighted mean of log H, converted back to the original scale.

of 10–20% even after 10–20 years." However, even then this may overestimate the decline in risk, since a number of studies give an estimated H of 10 to 20 years (see Table 7), and an increased risk of 10–20% after 10–20 years is more consistent with our overall estimate of H, than with the extreme at the high end. Note that an H of 4.41 predicts an increased risk of 21% after 10 years and 4% after 20 years.

4.4. Sources of heterogeneity and data limitations

We discuss below various factors that might have contributed to the observed variation between the estimates of H for the different blocks, and to the difficulties in fitting the negative exponential model. However, none of these offer a clear explanation for it.

4.4.1. Accuracy of recording of smoking habits

In case-control studies, time of quit is normally based on responses by the subject (or in some cases a proxy respondent) at or shortly after the time of diagnosis of the disease. These responses are subject to inaccuracy of recall, which itself may be affected by the diagnosis.

In prospective studies, time of quitting is normally based on responses given by the subject at baseline. While this again is open to inaccurate recall, it should not be biased by knowledge of disease, as the information is collected before onset of IHD. However, unless further interviews are carried out, which is rarely the situation, the reported RRs are based on the assumption that smoking status does not change during follow-up, ignoring the possibilities of later quitting by current smokers, and later restarting by quitters. Note that later starting by never smokers is a less important possibility in the populations studied.

4.4.2. Updating of time quit

A problem in prospective studies concerns the categorization of quitters by time of quitting. In most of the studies reporting results, risk is simply related to the time of quitting as reported at

baseline. Thus a subject classified as having quit for 5–9 years at baseline will still be counted as having quit for 5–9 years at time of IHD onset, which may be 10 to 20 years later. If risk declines monotonically with actual time of quitting, H will therefore be underestimated by the use of time of quitting as recorded at baseline. The extent of this bias is difficult to estimate, but will clearly increase with increasing time of follow-up, though it will be compensated to some extent by bias in the opposite direction if some of the quitters resume smoking during follow-up. As noted earlier two studies (DOLL and NURSES) did in fact update time of quit based on the latest information from repeat interviews, while two other studies (HRUBEC, WHITEH) updated time of quit in analysis, and one other study (HONJO) appeared to do so. However these studies still produced highly variable estimates of H (see Table 4), so this difference is not a ready explanation for the heterogeneity.

4.4.3. Reverse causation

For lung cancer and COPD, IARC report (2007) clear evidence that the risk in short-term quitters may be higher than in current smokers, this observation being assumed to be due to "reverse causation", with smokers quitting shortly before diagnosis as a response to precursor symptoms of the as yet undiagnosed disease. There seems to be evidence of this in a number of the data blocks we considered, though in some of these the observed increased risk in short-term quitters may be a chance finding, especially where there are few cases of IHD in this group. It should also be pointed out that, as noted earlier, short-term quitters were excluded from analysis in six blocks, and counted as current smokers in two, presumably as an attempt by the authors to avoid this bias. Our own sensitivity analyses suggests that reverse causation in fact has little effect on the estimated value of H, whether we excluded data from each block for the earliest quitting time, or we counted as current smokers all RRs within a block which related to a time of quitting of up to two years. This is probably due partly to the relatively small number of short-term quitters (as compared to current smokers) and partly to the estimation of H being more dependent on where the observed excess risk curve actually declines to half of that from current smoking than on the precise shape of the curve in the first year or so after quitting.

4.4.4. Age of the subjects and risk from current smoking

It is clearly established that the RR for current smoking decreases markedly with increasing age (Lee, 2001). Our analyses have shown that estimates of H significantly ($p < 0.001$) increase with increasing age of the subjects (at baseline in prospective studies), and also that estimates of H tend to be smaller where the current smoking RR was higher, though the significance of this association disappeared when age of the subject was already taken into account. One should be cautious about over-interpreting these data. One would expect precise estimation of H to be more difficult where the current smoking RR is low, a difficulty illustrated by the case of block 2 where the current smoking RR was less than 1.0, and the estimation procedure was unreliable. Also there may be a regression-to-the-mean effect, as chance over- or under-estimation of the current smoking RR will, for a given set of quitting RRs, correspondingly either under- or over-estimate H.

4.4.5. Estimating midpoints of time intervals

Another issue that should have an effect on the derived estimate of H is the accuracy of the estimated time midpoints we used for each quitting period. As the authors of the study never reported such midpoints, we had to provide our own estimates, usually derived as simple averages of the lower and upper extremes of the range. Our sensitivity analyses do not suggest that use of alternative fairly extreme midpoints for the open-ended final interval made much difference to the estimates of H, and certainly did not explain the observed heterogeneity between estimates.

4.4.6. Use of pseudo-numbers

Our methodology for fitting the negative exponential model requires knowledge, for each block, of the numbers of cases and the numbers of controls (or at risk) in each smoking group. As such data are not provided, and indeed for covariate-adjusted data do not exist in the strict sense, we used the method of Hamling et al. (2008) to estimate a set of pseudo-numbers which correspond exactly to the reported RRs and CIs. These pseudo-numbers have been shown to allow accurate estimation of RRs and CIs relative to a different base group from that used originally, and we believe should be an adequate basis for estimation of H and goodness-of-fit to the model. This issue seems to us likely to be of less concern than the other issues considered in the preceding paragraphs.

4.4.7. Adjustment for smoking variables

Our method requires a set of RRs comparing risk in current smokers, never smokers, and quitters by time of quit. For these to be comparable, the RRs have to be adjusted for the same set of variables, and as RRs relative to never smokers cannot be adjusted for smoking variables, such as amount smoked, we restricted attention to estimates that were adjusted for age and non-smoking characteristics. This is in some ways unfortunate as it meant excluding some analyses comparing risk of current smokers and quitters which were adjusted for smoking variables. Clearly smokers and quitters may differ by various smoking variables, as those who quit may be the less "intense" smokers. Similarly, there may be differences between those who quit for differing periods of time. To test whether estimates of H actually vary by other smoking variables using our methodology, one requires separate blocks of RRs where the current smokers and quitters are restricted to those with differing smoking habits. We identified four pairs of blocks where members of one pair were lighter smokers (<20 or <21 cigarettes per day) and members of the other pair were heavier smokers (20 or 21+ cigarettes per day) but found no evidence that estimates of H differed meaningfully between the lighter and heavier smokers.

4.4.8. Applying the model to studies of diseased patients

The main analyses are restricted to populations without specific diseases, mainly as we only found data for one study in a diseased population, and we were unsure whether or not the pattern of decline in risk following quitting varied by disease studied. Although the estimate of H for this study of HIV patients happened to be similar to our overall estimate, the data are clearly inadequate to determine whether disease status affects the pattern of decline.

4.5. Extending the negative exponential model to other diseases

The usefulness of the negative exponential model could be further tested by applying it to other diseases, including lung cancer, chronic obstructive pulmonary disease [COPD] and stroke. For lung cancer, there are a large number of relevant data sets and the higher RR for current smoking may afford better testing of the model. For lung cancer, the multistage is another model which predicts declines in excess risk following quitting (Lee, 1995), and it would be of interest to see how similar the estimates of H from the two models are.

4.6. A possible extension of the model

If the RR in current smokers is 1 + B, the negative exponential model predicts that the RR for quitters for time t will be 1 + B

exp ($-t \log_e 2/H$), with the ratio of excess risks, RER(t), given by exp ($-t \log_e 2/H$). Quitting can be viewed as switching from an exposure of F = 1 unit (that of current smokers) to an exposure of F = 0 units (that of quitters). Reexpressing RER(t) as $F + (1 - F)$ exp ($-t \log_e 2/H$) allows for the possibility of modelling the effects of switching to an exposure intermediate between 1 and 0. This may have applications in studying the effects of switching to a reduced number of cigarettes per day, or of switching to a reduced exposure product.

5. Conclusions

We identified 41 essentially independent data blocks from 23 studies, each block consisting of RRs for current smokers, never smokers and quitters by time of quit, expressed relative to either current or never smokers. Some studies provided separate blocks by sex, age or amount smoked. For each block, we fitted the decline in excess risk following quitting using the negative exponential model, and found that the fit was generally adequate, misfit in some blocks seemingly being due to block-specific unusual patterns in the data, rather than any consistent deficiency of the model. While we were able to derive a combined estimate for H of 4.40 (95% CI 3.26–5.95) years, there was considerable heterogeneity between blocks, with H estimated as less than 2 years in 10 blocks, and over 10 years in 12 blocks. Although H was found to increase ($p < 0.001$) with mean age at start of the study, no clear relationships were seen with study type, sex, or other block characteristics. Conclusions were little affected by sensitivity analyses relating to allowance for reverse causation, and to the estimates used in model-fitting for the final open-ended quitting period.

The negative exponential model has proved useful for fitting the pattern of decline in excess risk following quitting, and for summarizing patterns reported in different studies and data blocks within studies. Although fitted estimates of H vary between studies for reasons we cannot fully explain, and there are difficulties of fitting the model in the presence of reverse causation, our analyses strongly suggest that the conclusion by the US Surgeon General (1990) that "*the excess risk of CHD caused by smoking is reduced by about half after 1 year of smoking abstinence*" is inconsistent with the overall evidence, which we believe suggests a value of H more like 4 to 5 years.

The negative exponential model should be studied further. It could also prove useful for summarizing quitting data for lung cancer and other smoking-related diseases, and a modified version of it may help to summarize data from studies of the effects of reducing amount smoked, and of switching to reduced exposure products.

Conflict of interest statement

PNL, founder of P N Lee Statistics and Computing Ltd., is an independent consultant in statistics and an advisor in the fields of epidemiology and toxicology to a number of tobacco, pharmaceutical and chemical companies. This includes Philip Morris Products S.A., the sponsor of this study. JSF and JSH are employees of P N Lee Statistics and Computing Ltd.

Authors' contributions

PNL and JSF were responsible for planning the study. Literature searches were carried out by PNL with the assistance of JSH. Data entry was carried out by JSH and checked by PNL. Where appropriate, difficulties in interpreting published data or in the appropriate methods for derivation of RRs were discussed by all three authors. Statistical analyses were conducted by JSF along lines discussed and agreed with PNL. PNL drafted the paper, which was then critically reviewed by JSF and JSH.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.yrtph.2012.06.009.

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