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# Relative and absolute risk of colorectal cancer for individuals with a family history: A meta-analysis

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ABSTRACT

Accurate risk estimates for individuals with a family history of colorectal cancer are important for surveillance strategies. We systematically reviewed the literature on familial risks of colorectal cancer to determine relative risk estimates for categories of family history and translated these relative risk estimates into absolute risk estimates.

A random-effects meta-analysis pooled the effect estimates from individual studies and actuarial life-table methods converted relative into absolute risks. Fifty-nine studies were identified including 47 that estimated the relative risk of developing colorectal cancer given at least one affected first-degree relative. The pooled risk estimate was 2.24 (95% CI 2.06 to 2.43) which rose to 3.97 (95% CI 2.60 to 6.06) with at least two affected relatives. A population lifetime risk of 1.8% for a 50-year old increased to 3.4% (95% CI 2.8 to 4.0) with at least one affected relative or 6.9% (95% CI 4.5 to 10.4) with two or more. Accurate absolute risk estimates show how cancer risks vary over time, particularly by pattern of family history and age of individual at-risk.



## 1. Introduction

Colorectal cancer has the fourth highest cancer incidence in the world with many cases occurring in developed countries [1]. There were over 29,000 new diagnoses in England and Wales in 2000, so it currently accounts for over 11% of all cancer cases in both men and women in the UK [2]. The cloning of several high penetrance susceptibility genes for cancer in the past 15 years, such as *BRCA1* and *BRCA2* in breast cancer and *MLH1* and *MSH2* in colorectal cancer, has led to a greater awareness of family history as a risk factor for disease. The appropriate clinical management of individuals who present with a family history of colorectal cancer is dependent on the magnitude of the associated risk. For example, screening interventions such as colonoscopy or other enhanced surveillance techniques may be offered to individuals whose risk exceeds a predefined threshold [3]. Consequently, the accurate estimation of disease risk in individuals with different patterns of family history is essential.

Many epidemiological studies have estimated the risk of colorectal cancer in individuals with a family history of the disease [4]. Most of these studies have estimated the relative risk of disease, the ratio of disease incidence in those with a family history to those without, with estimates ranging from

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1.21- to 9.33-fold [5,6]. However, relative risk may not be the most useful risk measure in the context of individual counselling, as it requires comparison to a background population. A more appropriate estimate for healthcare purposes is absolute cumulative risk – the risk of a person with a family history developing (or dying from) colorectal cancer over a specific period of time.

Previous reviews have used meta-analysis to estimate familial risks associated with colorectal cancer, but they have not produced absolute risk estimates. Other studies have attempted to derive absolute risks, but have only used relative risk estimates taken from single studies and have not accounted for competing causes of mortality [7,8]. In this study, we aimed to synthesise the available evidence to obtain accurate estimates of age-specific relative risk for different family history categories, and to convert these relative risk estimates into absolute risks, taking into account competing causes of mortality.

## 2. Patients and methods

### 2.1. Literature search

Cohort, case-control and cross-sectional studies were eligible for inclusion if they quantified the risk of any type of colorectal cancer (ICD-10 codes C18.0–C21.0) in individuals with and without a family history, or if they presented sufficient raw data to directly estimate this relative risk. Studies were excluded if subjects were recruited from screening programs (as we believe that these people are more likely to have a family history than the general population); if cases or controls were selected on the basis of their family history; if controls had other malignant conditions; or if cases had only adenoma, familial adenomatous polyposis or hereditary non-polyposis colorectal cancer. Where multiple papers presented results from the same study (e.g. only one paper – either the most recent or most informative was included).

We identified potentially eligible studies published by January 2004 from three databases: MEDLINE, EMBASE and Dissertation Abstracts. The search strategy contained terms related to colorectal, colonic or rectal neoplasms, family, familial or family history, risk factors, and cohort, case-control, epidemiological, or observational studies (Appendix A). Reference lists of identified articles were searched to identify additional studies. No language restrictions were imposed.

### 2.2. Data extraction

We extracted information on the study population, study design and all relative risk estimates and associated levels of precision for inclusion in a database. From case-control or cross-sectional studies, we collected odds ratios (where presented), or calculated odds ratios and standard errors from raw data using standard methods [9]. Relative risks, familial hazard ratios or standard morbidity and mortality ratios were extracted from cohort studies and were all assumed to be good estimates of relative risk. Adjusted risk estimates were used where presented, if they were adjusted only for relevant confounders such as age. Otherwise unadjusted estimates or raw data were used for analysis. For sub-analyses we classified results according to category of family history, sex and age of affected relatives and individuals at-risk (cases and controls in case-control studies and relatives of cases and controls in cohort studies), site of cancer, study type and morbidity or mortality of patients. Where data were presented separately for discrete subgroups e.g. colon and rectum cancer, these were pooled using the Mantel–Haenzel method for raw data [10], or the inverse variance method for relative risks and confidence intervals.

### 2.3. Statistical methods

We performed both fixed-effect and random-effects meta-analysis using the inverse-variance weighting method [10,11]. Statistical heterogeneity between studies was assessed using the among-study variance ($\tau^2$) and the statistic $I^2$ [12]. Heterogeneity between subgroups was formally tested using meta-regression for study-level covariates or an interaction test for other variables. A sensitivity analysis was conducted to test the impact of each study on the heterogeneity by removing each study from the meta-analysis separately and recalculating the pooled estimates. A funnel plot and Egger's regression test for funnel plot asymmetry [13] were used to look for the presence of a small-study effect that might be due to publication bias. The Trim and Fill method was implemented to explore the possible nature of studies 'missed' in the review and to attempt to estimate the 'true' relative risk estimate accounting for publication bias [14]. All these analyses were undertaken using Stata version 8 (Stata Corporation, College Station, TX, USA).

We converted relative risk estimates into absolute cumulative risks by constructing life-tables. For baseline (general population) incidence of colorectal cancer diagnosis and mortality, we used age-group specific data for England and Wales in 2001, obtained from the Office of National Statistics [2]. We applied age-specific relative risk estimates to these incidence data to obtain incidence rates for individuals with a family history.

Life-tables were constructed using the approach described by Chiang [15]. First, we obtained age-specific incidence rates for colorectal cancer death and all-cause mortality (for the mortality analysis) or for colorectal cancer diagnosis and all-cause mortality (for the morbidity analysis) and combined these to produce a cumulative 'event' incidence for each age. We converted these to cumulative survival probabilities with the transformation: cumulative survival = $e^{(-\text{cumulative incidence})}$. Risks of colorectal cancer mortality or morbidity were obtained by applying incidence rates (for individuals with a family history) to cumulative survival probabilities. These risks were then summed to produce absolute cumulative risks over specific age ranges, and displayed graphically [16]. There are a number of assumptions made using this model, as described by Pharoah and Mackay [17].

The pooled relative risk estimates for the general population (1, by definition), for individuals with at least one affected first-degree relative (parent, sibling or offspring), and for individuals with at least two affected first-degree relatives were entered into the life-table. Graphs were generated to show the absolute risks of developing and of dying from colorectal cancer for these three categories of people over a 10-year

period, a 20-year period, and a lifetime (taken to be until age 70). Crude 95% confidence intervals for these absolute risk estimates were produced by entering the upper and lower confidence interval limits for the pooled relative risk estimates into the life-tables. All life-tables and graphs were produced using Microsoft Excel (Version 9.0).

## 3. Results

### 3.1. *Systematic review*

Fifty-seven papers were identified containing data from 60 different studies [5–8,18–70], 43 of which were case-control or cross-sectional studies (Table 1).

Twenty-one of the case-control studies used controls ascertained from the general population and 18 used hospital patients with non-malignant disorders as controls. The remaining four studies utilised a nested case-control or cross-sectional design where the family history of incident colorectal cancer cases in a prospective cohort was compared with that of disease-free controls taken from the same cohort.

Seventeen studies used either a prospective or retrospective cohort study design (Table 2). In four of these studies, cases were ascertained prospectively from a cohort without colorectal cancer at baseline, whilst the other 13 studies collected colorectal cancer cases and retrospectively compared the observed incidence in their relatives with that expected in the general population.

**Table 1 – Summary of case-control and cross-sectional studies included in analysis**

| Author | Year | Date | Place | Age[a] | Number of cases | Number of controls | Controls[b] |
|---|---|---|---|---|---|---|---|
| Adanja et al. [18] | 1995 | 1984–1993 | Serbia | 24–87 | 286 | 286 | H |
| Bonelli et al. [20] | 1988 | 1980–1986 | Italy | 26–91 | 414 | 855 | H |
| Borugian et al. [21] | 2002 | 1981–1986 | USA, China | ⩾20 | 473 | 1192 | P |
| Boutron et al. [22] | 1995 | 1985–1990 | France | 30–79 | 171 | 309 | P |
| Centonze et al. [24] | 1993 | 1987–1989 | Italy | Mean 67 | 119 | 119 | P |
| Chiu et al. [25] | 2003 | 1990–1993 | China | 30–74 | 931 | 1552 | P |
| Coogan et al. [26] | 2000 | 1983–1996 | USA | <70 | 1526 | 9653 | H |
| Coogan et al. (b) [26] | 2000 | 1992–1994 | USA | 20–69 | 1201 | 1201 | P |
| Diergaarde et al. [27] | 2003 | 1989–1993 | Netherlands | ⩽75 | 184 | 259 | P |
| Dora et al. [28] | 2003 | 1998–1999 | Russia | 40–79 | 663 | 323 | P |
| Duncan and Kyle [6] | 1982 | NS | UK | NS | 50 | 50 | H |
| Erlinger et al. [29] | 2004 | 1989–2000 | USA | >18 | 172 | 342 | NCC |
| Fisher and Armstrong [30] | 1989 | 1975–1985 | Australia | ⩾30 | 128 | 128 | H |
| Freedman et al. [31] | 1996 | 1982–1993 | USA | 34–88 | 163 | 326 | H |
| Ghadirian et al. [33] | 1998 | 1989–1993 | Canada | 35–79 | 402 | 688 | P |
| Keku et al. [40] | 2003 | 1996–2000 | USA | 40–79 | 676 | 1049 | P |
| Kerber et al. [41] | 1998 | 1994 | USA | 30–79 | 1993 | 2410 | P |
| Kim et al. [42] | 2003 | NS | Korea | Mean 57 | 125 | 247 | H |
| Kotake et al. [43] | 1995 | 1992–1994 | Japan | Mean 63 | 363 | 363 | H |
| Kune et al. [44] | 1989 | 1980–1981 | Australia | Mean 65 | 702 | 710 | P |
| La Vecchia et al. [45] | 1992 | 1985–1991 | Italy | <75 | 1222 | 1766 | H |
| Le Marchand et al. [46] | 1996 | 1987–1991 | USA | ⩽84 | 1192 | 1192 | P |
| Levi et al. [47] | 2002 | 1992–2000 | Switzerland | 26–74 | 286 | 550 | H |
| Maire et al. [50] | 1984 | 1979–1983 | France | 20–87 | 170 | 170 | H |
| Martinez et al. [51] | 1979 | 1973–1975 | Puerto Rico | ⩾20 | 461 | 461 | P |
| Minami and Tateno [52] | 2003 | 1997–2001 | Japan | ⩾40 | 488 | 2444 | H |
| Mitchell et al. [53] | 2004 | NS | UK | Mean 64 | 199 | 133 | P |
| Negri et al. [54] | 1998 | 1992–1996 | Italy | 23–74 | 1953 | 4154 | H |
| Nelson et al. [56] | 1994 | 1984–1987 | USA | 26–87 | 137 | 156 | H |
| Newcomb et al. [57] | 1999 | 1990–1991 | USA | <75 | 702 | 2274 | P |
| Pickle et al. [58] | 1984 | 1970–1977 | USA | Mean 74 | 86 | 176 | H |
| Ponz de Leon et al. [59] | 1989 | 1984–1986 | Italy | NS | 389 | 389 | H |
| Poole et al. [60] | 1999 | 1959–1972 | USA | ⩾30 | 2121 | 427,362 | NCC |
| Rozen et al. [61] | 1987 | 1979–1984 | Israel | Mean 46 | 148 | 936 | P |
| Sandhu et al. [62] | 2001 | 1993–1997 | UK | 45–74 | 151 | 30,202 | CS |
| Seow et al. [63] | 2002 | 1999–2000 | Singapore | ⩾40 | 121 | 222 | P |
| Slattery and Kerber [65] | 1994 | 1952–1992 | USA | All | 2473 | 7419 | P |
| Soliman et al. [66] | 1998 | 1996–1997 | Egypt | 16–75 | 111 | 111 | P |
| St John et al. [8] | 1993 | 1952–1985 | Australia | Mean 71 | 523 | 523 | H |
| Thun et al. [5] | 1992 | 1982–1988 | USA | ⩾30 | 1150 | 5746 | NCC |
| Woolf [68] | 1958 | 1931–1951 | USA | All | 242 | 242 | P[c] |
| Yang [69] | 1992 | 1988–1989 | China | <70 | 850 | 850 | P |
| Yoo et al. [70] | 1999 | 1988–1995 | Japan | ⩾20 | 372 | 21,061 | H |

a Age of study participants; NS, not stated.
b H, hospital controls; P, population controls; NCC, nested case-control study; CS, cross-sectional study.
c Controls were individuals who had died around the same time in the same county.

**Table 2 – Summary of cohort studies included in analysis**

| Author | Year | Date | Place | Age | Number of cases[a] | Follow-up[b] | Type[c] |
|---|---|---|---|---|---|---|---|
| Andrieu et al. [7] | 2003 | 1993–1998 | France | 25–95 | 766 | 117,407 | R |
| Bhatia et al. [19] | 1999 | 1971–1999 | USA | 8–19 | 25 | 18,908 | R |
| Carstensen et al. [23] | 1996 | 1982–1992 | Denmark | <60 | 1470 | 222,634 | R |
| Fuchs et al. [32] | 1994 | 1986–1992 | USA | 40–75 | 148 | 176,093 | P |
| Fuchs et al. (b) [32] | 1994 | 1982–1990 | USA | 30–55 | 315 | 663,936 | P |
| Goldgar et al. [34] | 1994 | 1952–1992 | USA | All | 4010 | NS | R |
| Hall et al. [35] | 1996 | 1987–1994 | UK | 30–45 | 65 | NS | R |
| Hall et al. (b) [35] | 1996 | 1987–1994 | UK | 37–88 | 212 | NS | R |
| Hemminki and Li [36] | 2001 | 1958–1996 | Sweden | ⩽61 | 4797 | NS | R |
| Jenkins et al. [37] | 2002 | 1992–1996 | Australia | 18–45 | 131 | 120,409 | R |
| Johns et al. [38] | 2002 | 1976–1978 | UK | <55 | 205 | NS | R |
| Karner-Hanusch et al. [39] | 1997 | NS | Austria | 26–90 | 100 | NS | R |
| Lovett [48] | 1976 | 1969–1973 | UK | 24–83 | 209 | NS | R |
| Macklin [49] | 1960 | 1952–1955 | USA | NS | 145 | NS | R |
| Nelson et al. [55] | 1993 | 1986–1990 | USA | 55–69 | 237 | 174,882 | P |
| Singh and Fraser [64] | 1998 | 1976–1982 | USA | >25 | 157 | 178,554 | P |
| Weber-Stadelmann et al. [67] | 1990 | 1982–1988 | Switzerland | 28–92 | 184 | NS | R |

a Number of colorectal cancer cases identified in cohort.
b Total person-years of follow-up. NS, not stated.
c R, retrospective study design; P, prospective study design.

Three papers each presented results from two different studies, however, Fuchs et al. [32] pooled their studies before analysis to give a combined relative risk estimate. All four studies from Hall et al. [35] and Coogan et al. [26] were included. Both Slattery and Kerber [65] and Goldgar et al. [34] reported on the same study, but non-overlapping data from both papers were used. This left 59 separate studies with risk estimates for meta-analysis.

### 3.2. *Relative risk given one first-degree relative affected with colorectal cancer*

Although all 59 studies estimated the relative risk associated with a family history of colorectal cancer, different definitions of family history were used. We focused on the category 'at least one affected first-degree relative' as this was the most commonly estimated and is also the most clinically relevant. Self-reported family history, as was mainly used in these studies, is also less likely to be accurate in more distant relatives [53].

Forty-seven studies reported the relative risk of developing colorectal cancer if at least one first-degree relative had been previously diagnosed with the same disease [6–8,19,20,22–24,26,28–35,37–41,43–48,50–55,57–63,67–70]. All studies showed a positive association with a range of relative risk estimates from 1.29 to 10.0, although in most studies the relative risk was between 1.5 and 4 (Fig. 1). The pooled relative risk estimate under a fixed effect model was 2.11 (95% CI 2.02 to 2.22), and under a random effects model was 2.24 (95% CI 2.06 to 2.43) ($P = 0.22$). As there was evidence for moderate heterogeneity between the studies ($I^2 = 54\%$, $\tau^2 = 0.033$) and the findings from the two models are not materially different, we chose to present random effects models for all analyses. No single study significantly affected the heterogeneity statistic when removed from the analysis (data not shown).

Inspection of the funnel plot suggests that there is a small-study effect with the smaller studies tending to have higher relative risk estimates, suggesting the presence of publication bias (Fig. 2(a)). Egger's regression test showed a significant small-study effect ($P = 0.001$) whilst the 'Trim and Fill' method suggested that 13 'missing' studies would need to be included to remove asymmetry from the funnel plot (Fig. 2(b)). With these hypothetical studies included, the relative risk having accounted for publication bias was estimated to be 2.07 (95% CI 1.89 to 2.26).

### 3.3. *Other family history categories*

The pooled risk estimate from all studies combined was 2.14 (95% CI 1.98 to 2.32), although this contains estimates based on different types of family history. Although most studies presented just the relative risk associated with having at least one affected first-degree relative, a few studies investigated alternative types of family history. The pooled relative risk estimate from the 13 studies that examined the risk associated with having any relative affected was 1.75 (95% CI 1.44 to 2.12). This category includes affected second-degree relatives (i.e., grandparents, aunts or uncles, or grandchildren) who carry a relative risk of 1.73 (95% CI 1.02 to 2.94) if at least one is affected (Fig. 3).

Having multiple affected relatives increases an individual's risk further. Meta-analysis of results from nine studies showed that having at least two affected first-degree relatives leads to a relative risk of 3.97 (95% CI 2.60 to 6.06) [7,8,32–34,45,54,57,62]. Two studies estimated the relative risk of having exactly two affected first-degree relatives, which was 5.44 (95% CI 4.34 to 6.82) when combined [7,8].

### 3.4. *Age-specific risk*

Four studies had relative risk estimates stratified by the age of the affected relative which could be classified as below 50 years and 50 years and above [23,36,38,62]. There was no significant difference between the pooled relative risk

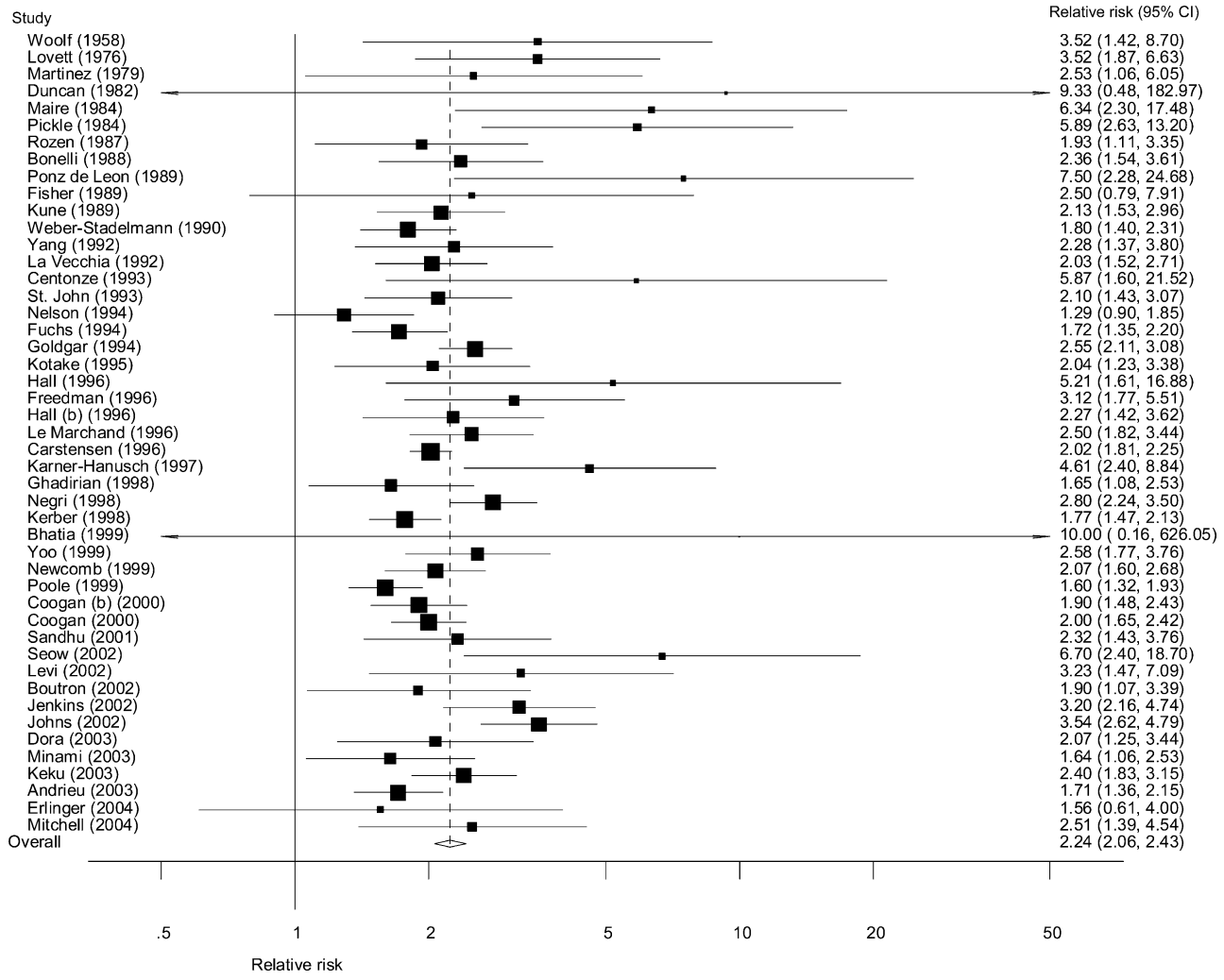


**Fig. 1 – Forest plot of the relative risk associated with having at least one first-degree relative with colorectal cancer. Each line represents an individual study result with the width of the horizontal line indicating the 95% CI, the position of the box representing the point estimate and the size of the box being proportional to the weight of the study.**

estimates with relatives below 50 giving a relative risk of 3.55 (95% CI 1.84 to 6.83) compared to 2.18 (95% CI 1.56 to 3.04) with those at or above 50 years of age ($P = 0.19$). Stratification by age of individual at-risk was available in 12 studies [7,8,23,32,33,36,38,44,46,54,57,62], which showed that the relative risk is significantly greater ($P = 0.003$) for younger relatives of affected individuals (subject < 50: relative risk 3.17, 95% CI 2.37 to 4.25; subject ⩾ 50: relative risk 1.90, 95% CI 1.59 to 2.28).

### 3.5. *Other factors*

Fig. 3 shows relative risk estimates for various types of at-risk individual with different numbers and sorts of affected relatives. A significant difference in relative risk estimates was seen between parents and siblings of affected individuals ($P = 0.005$), however, no other family history subgroups showed a significant difference at the 5% level. We also found no significant differences between the relative risk of developing or dying from colorectal cancer, or between cohort and case-control studies. The source of controls in case-control studies made some difference to the relative risk with population controls giving a lower estimate than hospital-based controls ($P = 0.05$), however, prospective cohort studies showed significantly lower relative risk estimates than retrospective studies ($P = 0.004$). There was no significant difference between the relative risk estimates for cancers in the colon or rectum, contrary to the results of individual studies.

### 3.6. *Absolute risks*

The relative risk estimates for the general population (1.00), individuals with at least one first-degree relative affected (2.24) and at least two first-degree relatives affected (3.97) were entered into the life-table. Cumulative absolute risk curves for developing colorectal cancer over 10 years, 20 years and by the age of 70 were produced (Fig. 4(a)–(c)). The probability of developing colorectal cancer over the next 10 years was less than 1% regardless of family history, until the age of 40, after which the risks increased up to age 75 to 2.5%, 4.7% (95% CI 4.0 to 5.6) and 9.6% (95% CI 6.3 to 14.2) for the general population, those with at least one affected

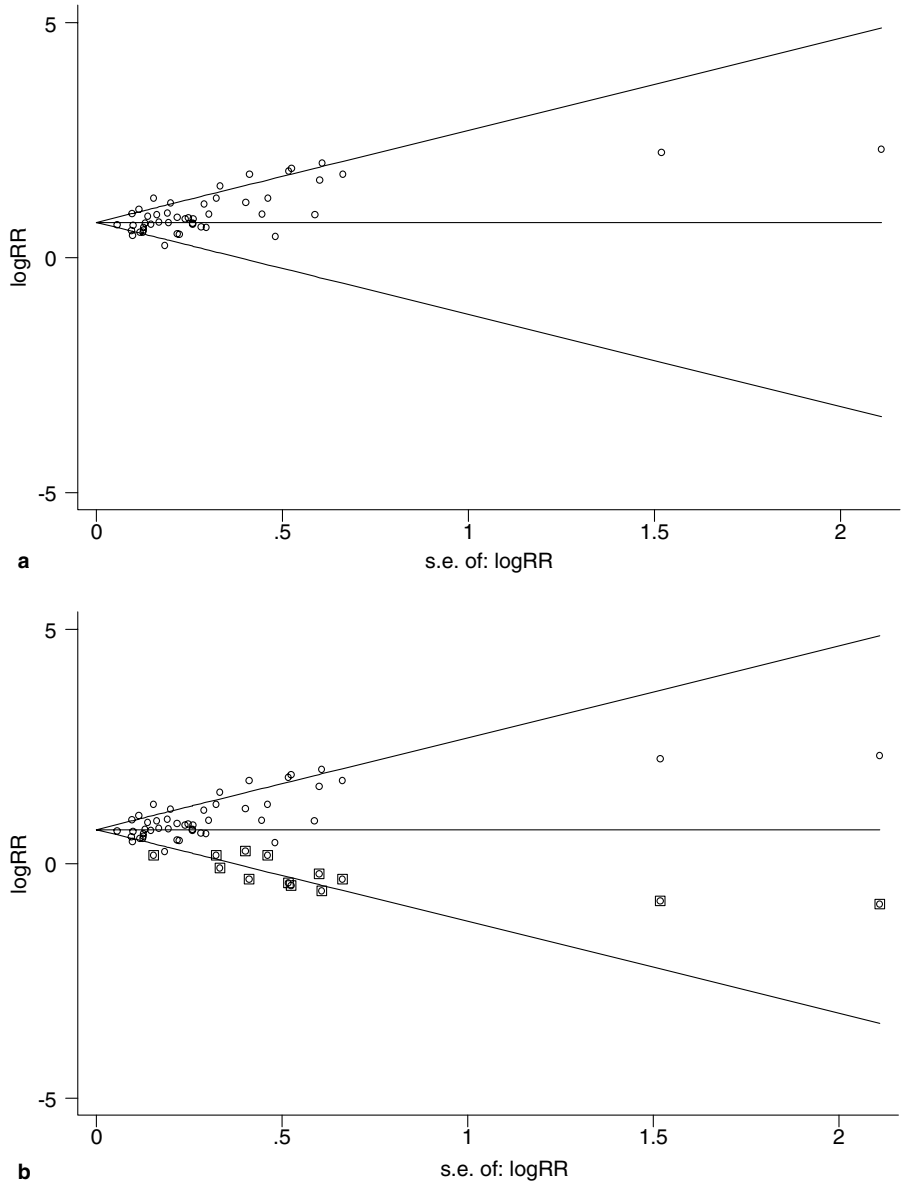


**Fig. 2 – Funnel plots of the log[RR*] and standard error (SE) of log[RR] for (a) each study, and (b) each study including 13 'missing' studies needed to correct asymmetry (in squares) estimated using the Trim and Fill method. The horizontal line represents the pooled estimate of log[RR] whilst the diagonal lines mark pseudo-95% CI limits. *RR = relative risk.**

first-degree relative and those with two or more affected first-degree relatives, respectively. The risks by age 70 also remain constant until around the age of 45 at 2.0% (1 in 50) for the general population, 3.6% (~1 in 30) for those with at least one first-degree relative with colorectal cancer and 7.4% (~1 in 14) for people with at least two affected first-degree relatives. These values decrease throughout middle age reaching zero risk at age 70.

The absolute risk curves for mortality from colorectal cancer are very similar to the morbidity curves (Fig. 4(d)–(f)). Until the age of 45, the cumulative risk by age 70 is 0.75% (~1 in 130) for the general population, 1.4% (~1 in 70) for individuals with at least one affected first-degree relative and 4.1% (~1 in 24) for those with two or more first-degree relatives with colorectal cancer.

### 3.7. *Effect of age of affected relative*

The absolute risks associated with having a first-degree relative affected below age 50 or at 50 and above were calculated using the corresponding relative risk estimates from the meta-analysis (Fig. 5). The risks were greater if the relative was diagnosed at a younger age, with a maximum 10-year morbidity risk of 8.6% (95% CI 4.6 to 15.9) seen at age 75. The cumulative risk by age 70 began at around 6.6% (~1 in 15) and remained above 4% (1 in 25) until the age of 60.

## 4. Discussion

We found 59 studies published between 1958 and 2004 that had estimated the relative risk of colorectal cancer given a

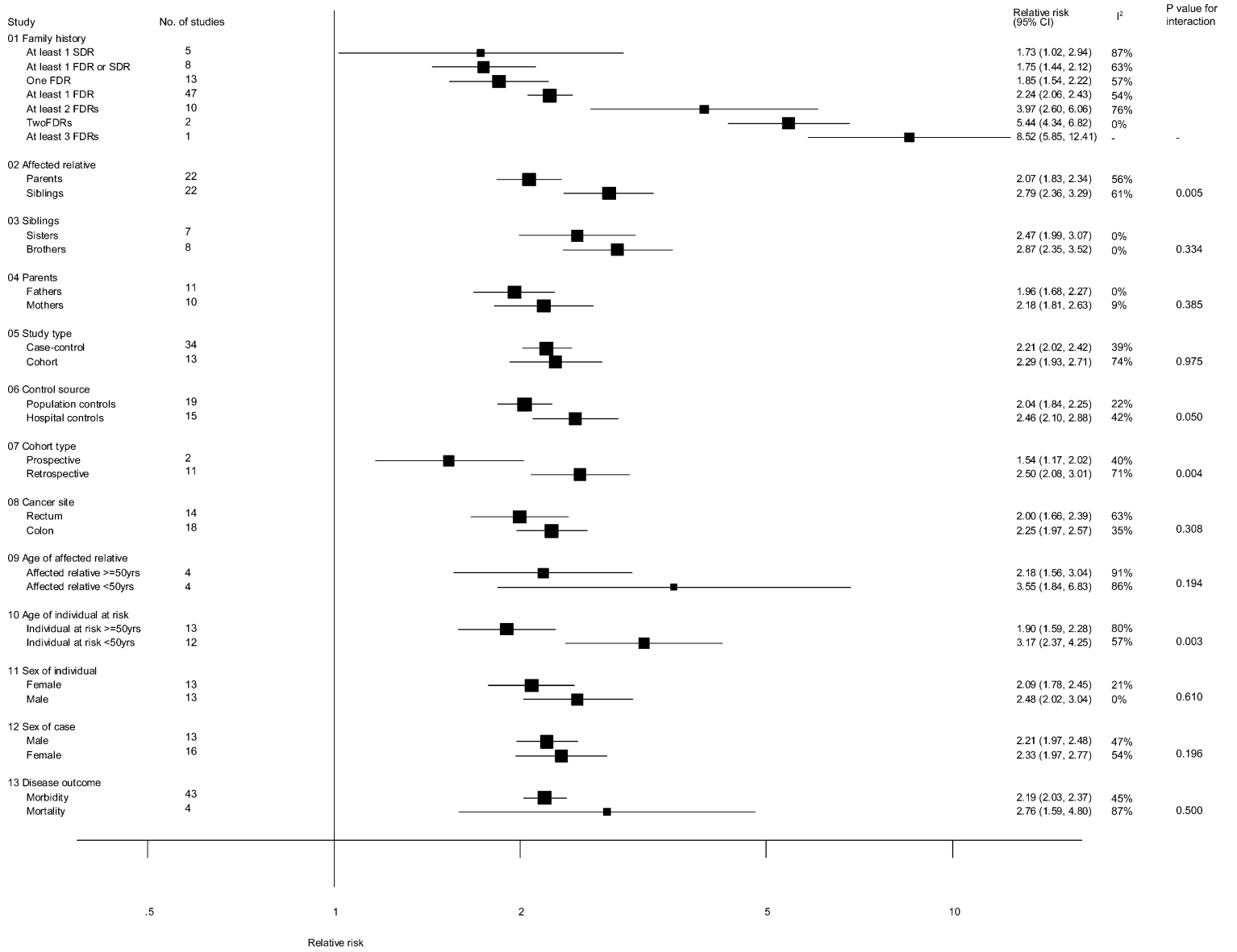


**Fig. 3 – Forest plot of the pooled relative risk estimates for subgroups of studies estimating the risk associated with having at least one affected first-degree relative. Each line represents a pooled subgroup risk estimate with the width of the horizontal line indicating the 95% CI, the position of the box representing the point estimate and the size of the box being proportional to the weight of each subgroup category.**

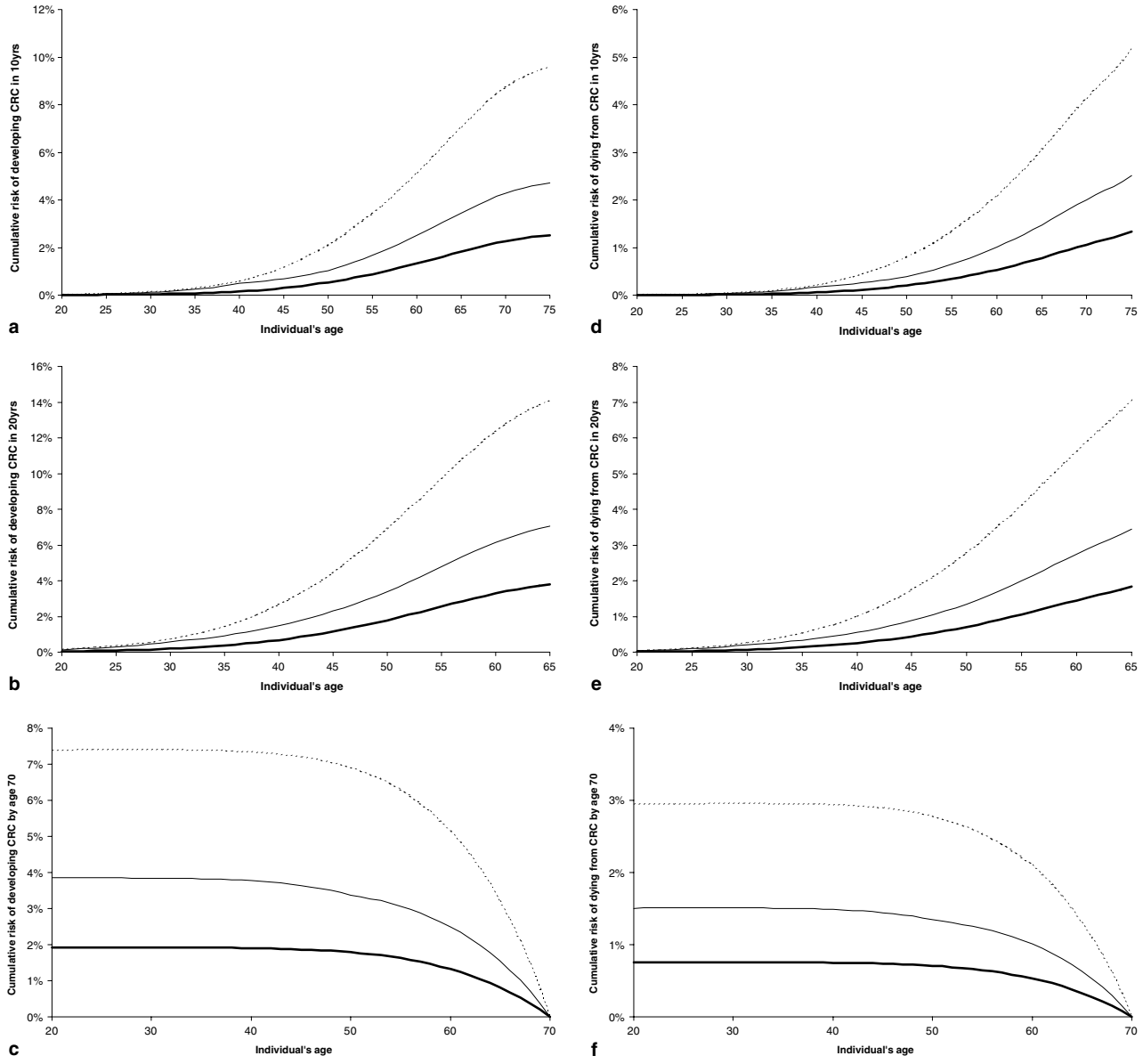


**Fig. 4 – Cumulative absolute risks of developing colorectal cancer over (a) 10 yrs, (b) 20 yrs, or (c) by age 70 and dying from colorectal cancer over (d) 10 yrs, (e) 20 yrs, or (f) by age 70. - - - - -, at least two first-degree relatives; ——, at least 1 first-degree relative; ——, general population. Note: graphs have different *X*- and *Y*-axes.**

familial background of the disease. A doubling of risk was seen when at least one first-degree relative was affected, which is equivalent to a 1 in 30 risk of developing colorectal cancer by the age of 70. Subgroup analyses showed that the age of the individual at-risk and the numbers of affected relatives also affect the risk of colorectal cancer.

The increased risk of a disease in a relative of an affected individual may be a result of hereditary factors, the consequence of a shared environment or a combination of the two. Whilst no attempt has been made in this study to assess the contribution of either of these causes, there is evidence that suggests that much of the risk is due to unknown heritable factors [71]. In this study, we found the sibling risk to be higher than the parent-offspring risk, which is suggestive of the presence of recessive genetic factors causing susceptibility to colorectal cancer.

The aim of this systematic review was to find all studies that had investigated the risk of developing, or dying from, colorectal cancer given a family history of the disease. Whilst it is difficult to establish whether this was achieved, the breadth of the search strategy and limited restrictions on the inclusion criteria lead us to believe that very few studies have been missed. Our efforts to find and include studies in which familial risk factors were not the primary outcome will also have reduced the potential for selection bias. A previous systematic review and meta-analysis found 27 studies published by 1999 [4]. The extra studies found in this systematic review (19 published since 1999 and 13 not included in the

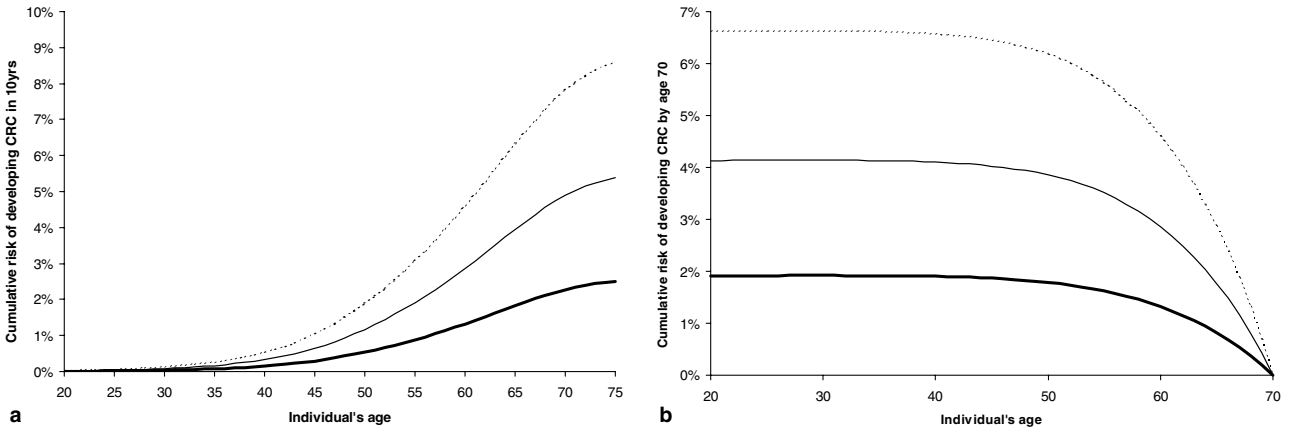


**Fig. 5 – Cumulative absolute risks of developing colorectal cancer over (a) 10 yrs or (b) by age 70 according to age of case diagnosis. ——, General population; ——, case diagnosed at or above 50 yrs; - - - - -, case diagnosed at less than 50 yrs. Note: graphs have different X- and Y-axes.**

previous review) add to the precision of the relative risk estimates produced, whilst also minimising the potential bias arising from failing to include all relevant studies. Although the pooled relative risk estimates found in this meta-analysis were similar to those found by Johns and Houlston, the larger dataset used in this review produced narrower confidence intervals around those estimates.

A variety of study designs, populations and risk measures were seen, although the majority of the studies were either case-control or retrospective cohort studies. There was no difference in effect size between case-control and cohort studies, however, the relative risk estimates from the prospective cohort studies were significantly lower than those from the retrospective studies. Although only two prospective studies investigated the risk associated with having at least one first-degree relative, the data from these studies may be more reliable as the likelihood of recall bias is reduced. This suggests that recall bias may inflate the relative risk estimates for both retrospective cohorts and case-control studies and therefore the summary estimates in this review.

Not all studies found had attempted to confirm the presence (or absence) of colorectal cancer in relatives using medical records or cancer registries. These studies had mostly assessed family history by questionnaire, either of the cases or their relatives. A potential bias is differential reporting of family history between cases and controls. However, a recent study from the UK has shown that colorectal cancer was underreported to the same degree by cases and controls [53], thus this is unlikely to be a substantial bias in our relative risk estimates. Despite the variation in case ascertainment amongst the studies, there is also little evidence of selection on the basis of family history which could bias the individual relative risk estimates.

Another potential bias in a systematic review is publication bias, where smaller studies show greater associations than larger (perhaps more recent) studies. This arises from non-publication of studies showing non-significant results which would reduce the pooled relative risk estimates if included in our meta-analysis. Evidence of possible publication bias was found in this meta-analysis, however, the measures we used to account for this indicated that the relative risk estimate is not being greatly inflated by the failure to include these missing studies. There was evidence of statistical heterogeneity between studies which could be caused by several factors. A proportion of the heterogeneity could be explained by the variation in study population characteristics, such as age, ethnicity or location. Each of these factors is known to affect an individual's probability of developing colorectal cancer, however, they will mainly influence the absolute risks that are more affected by the nature of the population at risk, and so we have assumed that the derived relative risk estimates are applicable to any population data. Differences in study design and category of family history studied also account for some proportion of the overall heterogeneity in risk estimates, although it is not clear which of these factors is the most important.

In deriving absolute risks for family history categories other than 'at least one affected first-degree relative', we assumed that the relative risk remains constant with increasing age (the proportional hazards assumption), and that the competing risk of all-cause mortality is the same for those with a family history as the general population. In addition, the risks should be interpreted in the context of the population of England and Wales from which the incidence and mortality data were derived. Although the absolute risks are not highly sensitive to slight changes in incidence or mortality rates, the background data could vary dramatically between populations and so extrapolation to individuals from other groups should be avoided.

The accuracy and variety of results in any meta-analysis are limited by the quality of the data being pooled. In this case, there were a good number of studies and participants from which to derive accurate risk estimates, however, there were limits to the analyses that could be done. Most studies used 'at least one affected first-degree relative' as their definition of family history so it was not possible to stratify the categories into those with exactly one first-degree relative versus those with more. There were also very few studies that had looked at extended family members e.g., second-degree relatives, and hence it was difficult to get an accurate assessment of how these relatives affect the risk.

This study adds to the evidence that having a first-degree relative affected with colorectal cancer approximately doubles the individual's risk of developing the same cancer compared to someone with no family history. We have also shown that having multiple affected relatives or being younger both increase that risk further. These relative risk estimates are translated into increases in absolute risk, although the magnitude of the increases vary depending upon the time-period specified. The absolute risk curves produced here can be used by healthcare professionals to accurately assess the risk of an individual with a family history of colorectal cancer developing or dying from the disease over the next 10 or 20 years, or by the age of 70. Using this information appropriate counselling, surveillance, or treatment can be administered based upon the most reliable and accurate available evidence.

## Conflict of interest statement

A.B. is funded by the Associated British Insurers which is a potential conflict of interest.

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## Appendix A. Search strategy

*Disease*

1 colon$
2 colon (MESH)
3 rectum
4 rectum (MESH)
5 rectal
6 colorect$
7 colorectal cancer
8 or/1–7
9 neoplas$
10 neoplasms (MESH)
11 cancer$
12 carcinoma$
13 carcinoma (MESH)
14 adenocarcinoma
15 adenocarcinoma (MESH)
16 nonpolyposis
17 colorectal neoplasms (MESH)
18 colonic neoplasms (MESH)
19 rectal neoplasms (MESH)
20 or/9–19

*Study*

21 case-control stud$
22 case-control study (MESH)
23 cohort stud$
24 cohort studies (MESH)
25 observational stud$
26 epidemiologic stud$
27 epidemiologic studies (MESH)
28 population stud$
29 family stud$
30 prospective stud$
31 prospective studies (MESH)
32 retrospective stud$
33 retrospective studies (MESH)
34 or/21–33

*Risk factors*

35 family
36 family (MESH)
37 familial
38 family history
39 risk factor$
40 risk factors (MESH)
41 or/35–40

*Combined search*

42 8 and 20 and 34 and 41

Limits: Human

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