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**Systematic review with meta-analysis of the epidemiological evidence relating smoking to type 2 diabetes**

Lee PN *et al*. Systematic review of smoking and type 2 diabetes

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# Abstract

BACKGROUND

Evidence relating tobacco smoking to type 2 diabetes has accumulated rapidly in the last few years, rendering earlier reviews considerably incomplete.

AIM

To review and meta-analyse evidence from prospective studies of the relationship between smoking and the onset of type 2 diabetes.

METHODS

Prospective studies were selected if the population was free of type 2 diabetes at baseline and evidence was available relating smoking to onset of the disease. Papers were identified from previous reviews, searches on Medline and Embase and reference lists. Data were extracted on a range of study characteristics and relative risks (RRs) were extracted comparing current, ever or former smokers with never smokers, and current smokers with non-current smokers, as well as by amount currently smoked and duration of quitting. Fixed- and random-effects estimates summarized RRs for each index of smoking overall and by various subdivisions of the data: sex; continent; publication year; method of diagnosis; nature of the baseline population (inclusion/exclusion of pre-diabetes); number of adjustment factors; cohort size; number of type 2 diabetes cases; age; length of follow-up; definition of smoking; and whether or not various factors were adjusted for. Tests of heterogeneity and publication bias were also conducted.

RESULTS

The literature searches identified 157 relevant publications providing results from 145 studies. Fifty-three studies were conducted in Asia and 53 in Europe, with 32 in North America, and seven elsewhere. Twenty-four were in males, 10 in females and the rest in both sexes. Fifteen diagnosed type 2 diabetes from self-report by the individuals, 79 on medical records, and 51 on both. Studies varied widely in size of the cohort, number of cases, length of follow-up, and age. Overall, random-effects estimates of the RR were 1.33 [95% confidence interval (CI): 1.28-1.38] for current *vs* never smoking, 1.28 (95%CI: 1.24-1.32) for current *vs* non-smoking, 1.13 (95%CI: 1.11-1.16) for former *vs* never smoking, and 1.25 (95%CI: 1.21-1.28) for ever *vs* never smoking based on, respectively, 99, 156, 100 and 100 individual risk estimates. Risk estimates were generally elevated in each subdivision of the data by the various factors considered (exceptions being where numbers of estimates in the subsets were very low), though there was significant (*P* < 0.05) evidence of variation by level for some factors. Dose-response analysis showed a clear trend of increasing risk with increasing amount smoked by current smokers and of decreasing risk with increasing time quit. There was limited evidence of publication bias.

CONCLUSION

The analyses confirmed earlier reports of a modest dose-related association of current smoking and a weaker dose-related association of former smoking with type 2 diabetes risk.

**Key words:** Smoking; Type 2 diabetes; Prospective studies; Meta-analyses; Dose-response; Review

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**Core tip:** Based on data from 145 follow-up studies of individuals free of type 2 diabetes at baseline, we confirm evidence of a modest association of smoking with subsequent onset of the disease. Meta-analysis showed relative risks of 1.33 [95% confidence interval (CI): 1.28-1.38] for current *vs* never smoking, 1.28 (95%CI: 1.24-1.32) for current *vs* non-smoking, and 1.13 (95%CI: 1.11-1.16) for former smoking. Risks increased with amount smoked and decreased with time quit. Elevated risks were consistently seen when the data were subdivided by various factors, suggesting that the associations are not a result of uncontrolled confounding.

# INTRODUCTION

Pan *et al*[1], 2015 published a meta-analysis and systematic review of the relationship of active, passive and quitting smoking with incident type 2 diabetes. Based on 88 prospective studies, they reported pooled relative risks (RRs) and 95% confidence intervals (CIs) compared to never smoking of 1.37 (95%CI: 1.33-1.42) for current smoking, 1.14 (95%CI: 1.10-1.18) for former smoking and 1.22 (95%CI: 1.10-1.25) for passive smoking, and evidence of a dose-relationship with amount smoked and years quit. This was an update of a previous review by the US Surgeon General, 2014[2], which based on 46 studies, had argued for a causal relationship. As evidence on tobacco smoking and type 2 diabetes has accumulated rapidly in the last few years, we wanted to investigate more extensively how this relationship may vary based on characteristics of the study or of the RR. We conducted our own updated review and meta-analysis, based solely on active smoking of cigarettes, with or without use of pipes, cigars or smokeless tobacco.

## MATERIALS AND METHODS

## *Study inclusion criteria*

Epidemiological prospective studies of populations without type 2 diabetes at baseline in which smoking was related to subsequent incidence of the disease.

The studies had to provide RR estimates for one or more defined major or dose-related smoking indices. The defined “major indices” compare ever, current or ex-smokers with never smokers, or current smokers with non-current smokers, and refer to smoking of any product (cigarettes, pipes, cigars and combinations) or to smoking of cigarettes. The defined “dose related indices” concern the amount currently smoked and the duration of quitting.

## *Study exclusion criteria*

Studies were excluded where the participants were restricted to those with diseases related to type 2 diabetes.

## *Literature searches*

This was carried out in five steps.

Step 1 identified relevant papers from four previously published reviews of evidence from relevant prospective studies. The review in the 2014 United States Surgeon-General Report[2], presented an analysis based on 46 prospective studies, taking into account studies reported in an earlier review by Willi *et al*[3], 2007 and adding additional studies. Since that Report, which included studies published up to 2010, two further meta-analyses have been published. That by Pan *et al*[1], 2015 included 88 studies, all but five of those considered by the United States Surgeon-General, along with many other studies published up to May 3, 2015. Another review by Akter *et al*[4], 2017 was limited to studies in Japan, and also considered studies up to 2015.

Step 2, carried out on January 31, 2019, repeated the Medline searches described by Pan *et al*[1], 2015, but with the search date restricted to January 1, 2015 onwards.

Step 3 was based on a search on our in-house reference system for papers with keywords DIABETES.

Step 4, carried out on March 1, 2019, repeated the Embase searches described by Pan *et al*[1], 2015, with the search restricted to papers not on Medline.

Finally, Step 5 was based on reference lists of papers identified in Steps 2, 3 and 4, looking for additional potentially relevant papers published from 2015.

In Steps 2 and 4, abstracts were examined first, with full texts obtained only for papers which appeared likely to be relevant. This step was initially carried out by Coombs KJ, with a 20% check made by Lee PN.

At each step, papers (or abstracts) examined for potential relevance were only those not previously considered.

At the end of this process, a set of potentially relevant papers was obtained. Subsequently, more detailed examination of the full texts at the data entry stage revealed that some papers did not actually meet the inclusion criteria, leading to a reduction in the list of relevant papers.

## *Data recorded*

Relevant information was entered onto a publication database and a linked RR database.

The publication database contains a record for each publication describing the following aspects: In-house reference ID of the publication; first author; publication year; location (continent/country); study name; study title; population studied; beginning and end year of baseline; end year of follow-up; length of follow-up; definition of type 2 diabetes (for both baseline exclusion and subsequent incidence) and source of diagnosis; cohort size; number of type 2 diabetes cases; age at baseline; sexes considered; races considered; definition of smoking; results available (current, former, ever, amount smoked, and years quit); details of results available for specific subsets [sex, age, body mass index (BMI), physical activity, alcohol, family history of type 2 diabetes, education, diet, and others]; and details of factors adjusted for in analyses (sex, age, BMI, physical activity, alcohol, family history of type 2 diabetes, education, diet, blood pressure, cholesterol, glucose, triglycerides, waist size, and others).

The RR database holds the detailed results, typically containing multiple records for each publication. Each record is linked to the relevant publication and refers to a specific comparison. The record includes details of the publication reference ID, study name, sex, age range at baseline, length of follow-up, BMI range, definition of smoking, and smoking status of the numerator (current, former or ever), and of the denominator (never or non). Where the smoking status is former, the range of years quit is entered. The range of amount smoked is also entered. For unadjusted RR estimates, the numbers of cases and at risk (or person years) are entered for both the numerator and denominator.

For adjusted RR estimates, the RR and 95%CI are entered, taken directly from the publication, or estimated using standard methods[5], with details also entered of the factors adjusted for.

Numbers of cases and at risk, or RRs and 95%CIs, are only entered for the whole population or for subgroups defined by sex, age group or BMI group. As noted above, the availability of results by other factors is recorded in the publication database, but the detailed results have not so far been entered. Results are also only entered unadjusted for potential confounding variables and adjusted for the most confounding variables for which results were available.

All data were entered by Coombs KJ and checked by Lee PN, with any disagreements discussed and resolved.

## *Multiple publications for the same study*

Once the data were entered, the list of publications was sorted into studies. Where the RRs from only one publication needed to be used in analysis, with the others providing no useful extra data (*e.g.*, providing similar data for a shorter follow-up), these “other” publications were rejected, with the reasons for rejection noted. Where more than one publication from the same study provided useful data (*e.g.*, for different aspects of smoking), one publication was nominated as the main reference for the study (typically, the publication providing the most detailed results) and others were nominated as subsidiary references. Thus, it was possible to have main, subsidiary and rejected references from the same study. Another possibility is that a publication may give a pooled analysis of several individual studies, including useful data for aspects not covered in the main publications of the separate studies. These pooled publications are also nominated as subsidiary references.

## *Meta-analyses*

Fixed-effect and random-effects meta-analyses were conducted using the method of Fleiss and Gross, 1991[6], with heterogeneity quantified by H, the ratio of the heterogeneity chisquared to its degrees of freedom. H is directly related to the statistic I2[7] by the formula I2 = 100 (H−1)/H. For all meta-analyses, Egger’s test of publication bias[8] was included.

## *The major smoking indices*

Meta-analyses were conducted using the available data for current *vs* never, current *vs* non, ever *vs* never, and former *vs* never smoking. Where there was a choice of estimates for a study, preference was given to results that were for the full range of amount smoked, the longest follow-up, the most adjusted, the widest age range, and the preferred product, with preference being given, in order to results for: Cigarettes; smoking excluding exclusive pipe/cigar; smoking; and tobacco; but not exclusive cigar, pipe or smokeless tobacco. For a study of both sexes, preference was also given to separate estimates for the two sexes, if available. While in most studies, the choice of estimates was straightforward, in others it was not (*e.g.*, between an unadjusted RR for a longer follow-up from one publication and an adjusted RRs for a shorter follow-up from another). Here Coombs KJ and Lee PN agreed and recorded the most relevant RR to choose (disregarding its magnitude). For a particular exposure (*e.g.*, current *vs* never) each study could provide only the estimate or two sex-specific estimates for inclusion in the meta-analysis.

Effect estimates were derived based on all the selected RRs as well as for those subdivided by various categorical variables: Sex (male, female, and sexes combined); continent (Asia, Europe, Americas, and Oceania); publication year (before 2005, 2005-14, 2015 or later); diagnosis of type 2 diabetes (self-reported, medical data only, both); population (general, pre-diabetics only, excludes pre-diabetics); total number of adjustment factors (0, 1-5, 6-10, 11+); cohort size (< 5000, 5000-20000, > 20000); number of type 2 diabetes cases (< 500, 500-999, 1000-2000, 2001+); highest baseline age (< 60, 60-74, 75+ years); length of follow-up (< 5, 5-10, > 10 years); definition of smoking [cigarettes, smoking (whether or not excluding exclusive pipe/cigar), tobacco]; and whether each of a range of different variables were adjusted for.

## *The dose-related smoking indices*

When comparing RRs by amount currently smoked (with a reference group of never smokers) or non-smokers, or by years quit (with a reference group of never smokers), a study typically provides a set of non-independent RRs for each dose-category, expressed relative to a common base. To avoid double-counting, it is necessary to include only one in any one meta-analysis.

For amount smoked, three methods were used. One method used only for studies that reported results for two levels of amount smoked, was to compare results for 1-19 and 20+ cigs/d, the most common subdivision used. The second, used only for studies that reported results for three levels of amount smoked was to compare results for low, medium and high cigs/d regardless of the levels selected. The third involved defining a set of key values (10, 20 and 40 cigs/d) and carrying out a separate meta-analysis for each key value. For an RR to be allocated to a key value its dose category had to include that key value and no other. This method was only applied for studies reporting results by three or more levels, with all three key value results available. These methods were used for data on current *vs* never smoking, and for current *vs* non-smoking.

For years quit, two methods were used. One simply used the shortest and longest categories. The other used the key values approach with values of 3, 7 and 12 years quit.

## *Results by BMI*

For each of the studies that reported independent RR estimates separately for different subdivisions of the population by level of BMI, estimates were made, for each smoking index for which data were available, of the ratio of the RR for highest *vs* lowest BMI group, these ratios then also being meta-analysed.

## *Avoidance of overlap*

When conducting meta-analyses care was taken to minimize overlap of cases. Thus, results from subsidiary papers were used only when the main paper did not provide the result required for the particular meta-analysis. Also, if an RR was available from three separate studies, and also from a combined analysis from the three studies, the individual results were preferred, only using the combined RR for a smoking index for which results were not reported in all the different studies.

# RESULTS

## *Publications and studies identified*

As summarized in Table 1[9-15], 221 publications were originally identified as likely to be relevant, with 42 later rejected during data entry, the reasons for rejection being given in Supplementary File 1. As seven of the publications provided results for two independent data sets (either presenting separate results for two studies or for two non-overlapping follow-up periods), data entry was carried out initially for 186 publication records. On investigation of studies with multiple records, 29 records were rejected as providing no useful information extra to those provided in other records) and 12 were classified as subsidiary, providing some limited extra information for records classified as main. This meant that there were 145 studies, 144 separate studies plus the combined analysis of three studies (HPFUS, NHS and NHSII). Table 2[9-14,16-161] summarizes some characteristics of these studies, while Supplementary File 1 also gives information on why some publications were rejected or only provided subsidiary information.

All stages of the identification of relevant papers, classification of papers with studies, and data entry were conducted initially by Coombs KJ and checked by Lee PN. Exceptionally, Lee PN only checked 20 percent of the abstracts for the Medline and Embase searches. This 20 percent check, of a total of 8798 hits, only resulted in four extra full-text papers being examined, only one of which proved to have relevant data. Given the very limited extra information obtained, and the time spent, it was decided not to extend this to a 100 percent check.

## *Study characteristics*

**Location:** As shown in Table 2, 53 of the 145 studies were conducted in Asia (including 23 in Japan, 10 in South Korea, nine in China and 11 in other countries). Fifty-three were conducted in Europe (eight in Great Britain, eight in Finland, seven in Germany, six in Sweden, five in Spain, and 19 in other countries), with 32 in North America (all in the United States), six in Australia and one in Brazil.

### **Population:** Ten of the studies were in females, 24 in males and 111 in both sexes. About half were of the relevant general population, with Table 2 showing further details.

**Time:** There was a clear increase in study frequency with time, with 17 starting before 1980, 23 starting in the 1980s, 47 in the 1990s, 42 in 2000-2005, and 16 from 2006 onwards.

### **Years follow up:** Twenty-four studies involved less than 5 years follow-up; 62 studies involved 5-9.9 years follow-up; 36 studies involved 10-14.9 years follow-up; and 23 studies involved 15 years or more years follow-up, with the longest (NOVAK) involving 35 years.

### **Diagnosis:** Fifteen of the studies diagnosed type 2 diabetes only on the basis of self-report of the individuals, 79 only on medical records, and 51 on both.

### **Size:** The numbers in the cohorts studied varied from 182 to over eight million. Sixty-three were under 5000, 39 in the range 5000 to 20000 and 43 larger than this.

### **Type 2 diabetes cases:** The number of type 2 diabetes cases varied from 27 to almost 180000. Eighty-two involved fewer than 500 cases, 21 involved 500-999 cases, 13 involved 1000-2000 cases, and 28 involved more than this. The number was not available for one study.

### **Age:** Most of the studies included some individuals of age 75 or older at baseline. However, 24 were restricted to those aged less than 60 and 30 more were restricted to those aged less than 74.

## *Meta-analyses*

### **Current *vs* never smoking:** The studies provided 99 RR estimates from 80 studies for the comparison of current *vs* never smoking. Nineteen studies provided estimates for both sexes, six for females only, 17 for males only and 38 only for sexes combined. Of the 99 estimates, 12 were below 1, 10 were above 2, with the remaining 77 in the range 1 to 2. The overall fixed-effect RR estimate was 1.25 (95%CI: 1.24-1.26) with highly significant heterogeneity between the estimates (Chisq. 816.8 on 98 df, *P* < 0.001, I2 = 88.0%). The random-effects estimate was somewhat higher at 1.33 (95%CI: 1.28-1.38). There was limited evidence of publication bias (0.01 < *P* < 0.05).

Table 3 presents the overall random-effects estimate, together with a breakdown of the estimates by various factors, with fuller details given in Supplementary File 2. There was evidence (*P* < 0.05) that the estimates varied by population type with both the estimates from studies restricted to pre-diabetics exceeding 3. There was also evidence that estimates were higher in those that were more adjusted (*P* < 0.05) or adjusted for various other individual factors (age, alcohol, family history of diabetes, cholesterol, triglycerides – all *P* < 0.05 - and glucose – *P* < 0.01), but were lower in those that were adjusted for education (*P* < 0.05). It is notable, however, that with the exception of two estimates based on less than five RRs, all the RR estimates shown in Table 3 were significantly (*P* < 0.05) increased.

For the analysis subdivided by sex, Figure 1 (females), Figure 2 (males) and Figure 3 (sexes combined) summarize the data in forest plots, while Figure 4 (females), Figure 5 (males) and Figure 6 (sexes combined) present funnel plots to illustrate possible publication bias. No marked publication bias was evident.

Table 4 (and Supplementary File 3) summarizes the results of the dose-response analysis for current *vs* never smoking. Whichever of the three methods of dose-response grouping was used, the RR estimates clearly rose with increasing amount smoked, and the increase at each level remained significant (*P* < 0.05). Note that the sets of estimates are not independent, with all the studies providing results for the key value analysis also contributing to the low/medium/high split.

### **Current *vs* non-smoking:** There were 156 RR estimates from 133 studies for the comparison of current *vs* non- smoking. Twenty-three studies provided estimates for both sexes, eight for females only, 24 for males only and 78 for sexes combined.

Of the 156 estimates, 27 were below 1, 11 were above 2, with the remaining 118 in the range 1 to 2. The overall fixed-effect RR estimate was 1.20 (95%CI: 1.20-1.21), with highly significant heterogeneity (Chisq. 1986.7 on 155 df, *P* < 0.001, I2 = 92.2%), and the random-effects estimate was 1.28 (95%CI: 1.24-1.32), slightly lower than the estimate for current *vs* never smoking. As for current smoking, there was limited evidence of publication bias (0.01 < *P* < 0.05).

Table 3 also presents the overall random-effects estimate for current *vs* non-smoking, as well as a breakdown of the estimates by different factors (see also Supplementary File 4). As for current *vs* never smoking, the random-effects estimate was elevated in all subdivisions of the data, significantly so except where based on very few estimates. There was little evidence of variation in the RR in subdivisions of the data by level of the various factors studied, the most notable exceptions being the somewhat higher estimate in studies adjusted rather than unadjusted for family history of diabetes, and the variation by continent.

Table 4 (and Supplementary File 5) summarizes the results of the dose-response analysis for current *vs* non-smoking. As for current *vs* never smoking, there was clear evidence that risk rises with amount smoked, whichever dose-response grouping is used.

Forest and funnel plots for the analysis subdivided by sex are shown in Supplementary File 6.

### **Former *vs* never smoking:** There were 100 RR estimates from 81 studies for the comparison of former *vs* never smoking. Nineteen provided estimates for both sexes, seven for females only, 17 for males only and 38 for sexes combined.

Of the 100 estimates, 18 were below 1, 7 were above 2, with the remaining 75 in the range 1 to 2. The overall fixed-effect estimate was 1.09 (95%CI: 1.08-1.10), with highly significant heterogeneity (Chisq. 263.6 on 99 df, *P* < 0.001, I2 = 62.4%). The random-effects estimate was 1.13 (95%CI: 1.11-1.16). Somewhat stronger evidence of publication bias (0.001 < *P* < 0.01) was seen than for current smoking.

Table 5 presents the overall random effects estimate, together with a breakdown of the estimates by different factors (see also Supplementary File 7). There was no strong evidence (*P* < 0.01) of variation in the RR by level of any factor, with estimates slightly elevated in all subgroupings except where based on very few estimates.

Table 6 (and Supplementary File 8) summarizes the results of the dose-response analysis for former *vs* never smoking. These showed clear evidence that the RR declined with increasing time since quitting.

Again, forest and funnel plots are shown in Supplementary File 6.

### **Ever *vs* never smoking:** One hundred RRs were available from 82 studies. The overall fixed-effect RR estimate was 1.17 (95%CI: 1.16-1.18) with evidence of considerable heterogeneity (Chisq. 897.37 on 99 df, *P* < 0.001, I2 = 89.0%), the random-effect estimate being 1.25 (95%CI: 1.21-1.28). There was some evidence of publication bias (0.001 < *P* < 0.01). RRs were generally elevated in all subgroups, the strongest evidence of variation by any factor (*P* < 0.001) relating to adjustment for education, unadjusted estimates (RR = 1.29, 95%CI: 1.24-1.34) being higher than adjusted ones (RR = 1.17, 95%CI: 1.12-1.21). There was also weaker evidence (*P* < 0.05) that RRs were somewhat higher in Asia, and somewhat lower in populations with a baseline upper age limit of 75 or more, or if the RRs were unadjusted for glucose. See Table 8 and Supplementary File 9 for fuller details.

Only one of the studies provided information on risk by amount smoked, so no dose-response meta-analyses were possible.

Again, forest and funnel plots are shown in Supplementary File 6.

### **Ratio of RRs for highest to lowest BMI groupings:** Six studies provided results by level of BMI, three of these giving results for each sex separately. One study provided data only for current *vs* never and former *vs* never smoking, while the others also provided data for current *vs* non-smoking and ever *vs* never smoking. None of the meta-analyses provided any evidence of variation in RR by level of BMI, the random effects meta-analysis estimate of the highest to lowest ratio being 1.20 (95%CI: 0.92-1.57) for current *vs* never smoking, 1.06 (95%CI: 0.82-1.36) for current *vs* non-smoking, 1.12 (0.95-1.32) for former *vs* never smoking, and 1.03 (95%CI: 0.87-1.23) for ever *vs* never smoking, based on, respectively, 9, 7, 9 and 7 estimates. (See Supplementary File 10).

***Supplementary files***

Supplementary File 1 gives further details of the literature search, including a list of the 42 publications rejected during data entry, giving the reasons for rejection, and a description of how multiple publications from a study were dealt with.

Supplementary Files 2, 4, 6 and 8 give full details of the results for the main analysis of, respectively, current *vs* never smoking, current *vs* non-smoking, former *vs* never smoking and ever *vs* never smoking. Each file is laid out similarly. Introductory pages describe the content and layout of the output, and explain the abbreviations used and the decisions made where multiple results were available for a single study. Table 1 of each Supplementary File then gives details of each candidate RR selected from the main and subsidiary publications for each study, while Table 2 of each file gives details of the RRs actually used in the analyses, and Tables 3-27 of each file give full results of the meta-analyses subdivided by each of the 25 factors considered (sex, continent, *etc.*).

Supplementary Files 3, 5 and 7 give full details of the dose-response analysis of respectively, current *vs* never smoking (by amount smoked), current *vs* non- smoking (by amount smoked) and former *vs* never smoking (by year quit). Each file includes separate blocks of description and results, similar to those for Supplementary Files 2, 4 6 and 8, but only including Tables 1-3 of those files, with Table 3 only showing results subdivided by sex. Each block relates to a specific dose-response level (*e.g.*, about 10 for amount smoked).

Supplementary File 9 gives the results of meta-analyses of ratios of relative risks for the highest to lowest BMI groupings available.

Supplementary File 10 presents forest and funnel plots for current *vs* non-smoking, former *vs* never smoking and ever *vs* never smoking, similar to those shown in Figures 1-6 of the paper for current *vs* never smoking.

# DISCUSSION

According to the United States National Institute of Diabetes and Digestive and Kidney Diseases Health Information Center[162], risk factors for type 2 diabetes include overweight/obesity, age, a family history of diabetes, high blood pressure, low high-density lipoprotein cholesterol, high triglycerides, a history of gestational diabetes, giving birth to a baby weighing 9 pounds or more, physical inactivity, a history of heart disease or stroke, as well as being in certain ethnic groups or having certain diseases. Smoking is not mentioned as a risk factor.

The meta-analyses we conducted indicate a modest relationship of smoking to risk of type 2 diabetes. This can be seen for current smoking (whether compared with never or non-smokers), former smoking and ever smoking. While there was clear evidence of heterogeneity in the RRs, the random-effects RRs showed increased risks in males and females, in younger and older subjects, in all continents studied, regardless of the basis of diagnosis, and regardless of the definition of smoking used. Despite the evidence of heterogeneity between the individual estimates, a striking feature of the results presented in Tables 3 and 5 was the fact that the estimates were elevated in virtually every subdivision of the data, whichever factor the subdivision was based on. There was also clear evidence (see Tables 4 and 6) of an increasing risk with increasing amount smoked by current smokers and of decreasing risk with increasing time quit by former smokers. Though there was some evidence of variation in risk by level of some factors, this did not suggest that the elevation in risk was unique to some populations or could be explained by adjustment for specific confounding variables. Nor did the fact that some studies did not report an elevation affect the overall conclusion. With a relatively weak association (with RRs about 1.3 for current smoking and about 1.13 for former smoking) it might be expected that some smaller studies would not detect an elevated risk. However, this did not affect the overall conclusion. Indeed, it was notable that, of the 12 RR estimates for current *vs* never smoking that were below 1.0, only one was statistically significant (at *P* < 0.05), whereas, of the 87 estimates above 1.0, as many as 63 were.

Given the weight of evidence from this review and others, smoking may be a contributory factor to type 2 diabetes. Publication bias, for which some evidence was detected, might have led to some over-estimation of the association, due to some studies finding no relationship not presenting their results. Bias due to misclassification of smoking status would only tend to bias the observed relationship down, not produce an association that did not truly exist. Failure to control properly for diet, BMI or related factors would not seem to be an explanation of the association as elevated risks were seen in studies that adjusted for these factors. That said, it is clear from Table 3 that many of the studies did not adjust for various factors listed in the first paragraph of the discussion, so that the association seen between smoking and type 2 diabetes may have suffered from uncontrolled confounding to some extent.

This review has limitations, some unavoidable. Lack of access to individual person data limited the detail of the meta-analyses that can be carried out, but obtaining such data was not practical. Obtaining a reliable definition of outcome, exposure and adjustment variables was sometimes hindered by incomplete information in the source papers. Some studies involved relatively few type 2 diabetes cases, but associations were evident both in studies with small and large numbers. It is possible that our analyses did not make full use of all the data collected, but this is inevitable in a paper of reasonable length. We would be willing to make our database available to bona fide researchers for further analysis.

Our results are consistent with those of the earlier review by Pan *et al*[1] based on 88 prospective studies. Although our analyses were based on a considerably larger number of studies, 145, our estimated random-effect RRs of 1.33, 1.28 and 1.13 for current *vs* never, current *vs* non, and former *vs* never smoking were similar to their corresponding estimates of 1.40, 1.35 and 1.14. Like us, they also found dose-response relationships with amount smoked and years since quitting. The interested reader is referred to that paper for further discussion of limitations of the data and interpretation of the results.

That paper refers to “the high prevalence of smoking in many countries and the increasing number of diabetes worldwide” and considers that “reducing tobacco use should be prioritized as a key public health strategy to prevent and control global epidemic of diabetes”. Though reduction of smoking is clearly important to limit a range of diseases such as lung cancer, chronic obstructive pulmonary disease and cardiovascular disease, one must question this prioritization, in the light of the range of other risk factors for type 2 diabetes noted above, and the evidence that diabetes incidence is rising fast worldwide[56], while smoking is declining[2]. As a strategy, controlling diet may be much more beneficial. The work of Taylor *et al*[163] suggests that, in many people, type 2 diabetes can be completely reversed quite rapidly by appropriate diet and weight loss.

# In conclusion, the analyses confirm earlier reports of a modest dose-related association of current smoking and a weaker dose-related association of former smoking with risk of type 2 diabetes.

# ARTICLE HIGHLIGHTS

## *Research background*

A systematic review of the relationship between smoking and incident type 2 diabetes, based on 88 epidemiological prospective studies, was published in 2015. Much new evidence on this relationship has become available since then.

## *Research motivation*

To obtain up-to-date evidence relating smoking to type 2 diabetes.

## *Research objectives*

To systematically review available evidence from prospective studies on the relationship of type 2 diabetes onset to ever, current or former smoking of cigarettes or of any tobacco product, including dose-response data.

## *Research methods*

Attention was restricted to prospective studies of populations free of type 2 diabetes at baseline which related subsequent incidence of the disease to one or more defined major or dose-related smoking indices. The major indices compared ever, current or former smokers to never smokers and current smokers to non-current smokers. The dose-related indices concerned amount currently smoked and years quit. Literature searches identified relevant papers from previous reviews, from Medline searches and from references lists of relevant papers identified. Data were extracted on study details and on the relative risks required, estimated if required using standard methods. Care was taken to avoid overlap of data from the same study from multiple publications. Fixed-effect and random-effects meta-analyses were conducted, including tests of heterogeneity and publication bias. Where a study provided multiple estimates, a preference scheme was used involving factors such as level of adjustment for confounding factors, length of follow-up and age range considered. Sex-specific results were used, if available. Effect estimates were derived based on all the selected RRs, and also for those subdivided by various categorical variables – sex, continent, year of publication, basis of diagnosis of diabetes, initial diabetes status of the population, age, length of follow-up, definition of smoking, and whether a range of different variables were adjusted for.

## *Research results*

The literature searches identified 157 relevant publications providing results from 145 studies. Overall random-effect RR estimates were 1.33 [95% confidence interval (CI): 1.28-1.38] for current *vs* never smoking, 128 (95%CI: 1.24-1.32) for current *vs* non-smoking, 1.13 (95%CI: 1.11-1.16) for former *vs* never smoking and 1.25 (95%CI: 1.21-1.28) for ever *vs* never smoking, each combined estimate being based on at least 99 individual estimates. Estimates were generally elevated in each subdivision of the data by the categorical variables considered, though in some cases RR estimates varied significantly (*P* < 0.05) by level. The dose-response analysis showed that risk increased with increasing amount smoked, and reduced with increasing time quit.

## *Research conclusions*

Our analyses confirmed and extended reports of a modest dose-related association of current smoking and a weaker dose-related association of former smoking with risk of type 2 diabetes. The evidence suggests smoking may contribute to the risk of type 2 diabetes, though our estimates may be affected by publication bias and some uncontrolled confounding. Although reduction of smoking is clearly important to limit risk of diseases such as lung cancer, chronic obstructive pulmonary disease and cardiovascular disease, the worldwide rise in incidence of type 2 diabetes, coupled with a decline in smoking, suggests that control of other factors, such as diet, may be much more beneficial in reducing type 2 diabetes risk.

***Research perspectives***

Our analyses suggest strongly that there is a modest increased risk of type 2 diabetes associated with current smoking which is greater in heavier smokers and reduced following quitting. Further large prospective studies could characterize this more precisely by more detailed assessment of smoking history and by more fully accounting for the range of other factors known to be related to type 2 diabetes. Care should be taken to determine the accuracy of all the data used, and to assess the effect that any possible inaccuracy might have on the estimated association.

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**Footnotes**

**Conflict-of-interest statement:** The authors have carried out consultancy work for many tobacco organizations.

**PRISMA 2009 Checklist statement:** The guidelines of the PRISMA 2009 statement have been adopted.

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**Figure Legends**



**Figure 1 Forest plot for current *vs* never smoking, results for females.** For each selected relative risk (RR), the figure shows the study ref. (see Table 2) and the RR and 95% confidence interval, both numerically and plotted as a line on a log scale from 0.1 to 10. The RRs are plotted from highest to lowest, with the RR estimate shown in the centre of the line as a square, with area proportional to the weight of the estimate. Lines showing RRs with wide confidence intervals may be truncated, as indicated by an arrow head at the truncated end. Also shown are the overall fixed-effect and random-effects estimates. The vertical line is at RR = 1 with an increased risk indicated by a preponderance of squares to its right.RR: Relative risk; CI: Confidence interval.



**Figure 2 Forest plot for current *vs* never smoking, results for males.** For each selected relative risk (RR) the figure shows the study ref. (see Table 2) and the RR and 95% confidence interval, both numerically and plotted as a line on a log scale from 0.1 to 10. The RRs are plotted from highest to lowest, with the RR estimate shown in the centre of the line as a square, with area proportional to the weight of the estimate. Lines showing RRs with wide confidence intervals may be truncated, as indicated by an arrow head at the truncated end. Also shown are the overall fixed-effect and random-effects estimates. The vertical line is at RR = 1 with an increased risk indicated by a preponderance of squares to its right. RR: Relative risk; CI: Confidence interval.



**Figure 3 Forest plot for current *vs* never smoking, results for sexes combined.** For each selected relative risk (RR), the figure shows the study ref. (see Table 2) and the RR and 95% confidence interval, both numerically and plotted as a line on a log scale from 0.1 to 10. The RRs are plotted from highest to lowest, with the RR estimate shown in the centre of the line as a square, with area proportional to the weight of the estimate. Lines showing RRs with wide confidence intervals may be truncated, this being indicated by an arrow head at the truncated end. Also shown are the overall fixed-effect and random-effects estimates. The vertical line is at RR = 1 with an increased risk indicated by a preponderance of squares to its right. RR: Relative risk; CI: Confidence interval.



**Figure 4 Funnel plot for current *vs* never smoking, results for females.** Each of the selected relative risks (RRs) is shown as a diamond, plotted against its value on the x-axis (on a log scale) and the standard error of loge RR on the y-axis. The vertical line indicates the overall fixed-effect estimate, while the diagonals indicate where 95% of the values should lie, given the standard error of loge RR. Evidence of publication bias is indicated by a tendency for the smaller (high standard error) studies to show larger treatment effects. RR: Relative risk.



**Figure 5 Funnel plot for current *vs* never smoking, results for males.** Each of the selected relative risks (RRs) is shown as a diamond, plotted against its value on the x-axis (on a log scale) and the standard error of loge RR on the y-axis. The vertical line indicates the overall fixed-effect estimate, while the diagonals indicate where 95% of the values should lie, given the standard error of loge RR. Evidence of publication bias is indicated by a tendency for the smaller (high standard error) studies to show larger treatment effects. RR: Relative risk.



**Figure 6 Funnel plot for current *vs* never smoking, results for sexes combined.** Each of the selected relative risks (RRs) is shown as a diamond, plotted against its value on the x-axis (on a log scale) and the standard error of loge RR on the y-axis. The vertical line indicates the overall fixed-effect estimate, while the diagonals indicate where 95% of the values should lie, given the standard error of loge RR. Evidence of publication bias is indicated by a tendency for the smaller (high standard error) studies to show larger treatment effects. RR: Relative risk.

##### Table 1 Literature searching

|  |  |  |  |
| --- | --- | --- | --- |
| **Step** | **Papers originally selected as probably relevant1** | **Papers rejected during data entry2** | **Papers providing separate results for multiple studies3** |
| 1 | Previous reviews | 98 | 10 | 3[9-11] |
| 2 | Medline search | 74 (from 3365 hits) | 23 | 4[12-15] |
| 3 | In-house database | 1 | 0 | 0 |
| 4 | Embase search | 33 (from 5433 hits) | 7 | 0 |
| 5 | Secondary references4 | 15 (of 30 identified) | 2 | 0 |
| Total | 221 | 42 | 7 |

1Numbers of papers originally selected exclude those already identified in a previous step. 2Reasons for rejection are summarized in Supplementary File 1. 3Or for separate periods of follow-up. 4From papers identified in steps 2 to 4.

##### Table 2 Some characteristics1 of the 145 studies of smoking and type 2 diabetes

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study Ref.** | **Main Ref.** | **Other Ref.** | **Continent** | **Country, location2** | **Study Population3** | **Sex** | **Baseline** | **Follow-up (yr)4** | **Diagnosis Code5** | **Cohort size** | **Diabetes cases** | **Age** |
| 3 studies6 | [16] |  | North America | United States | Medical professionals | M+F | 1984-1991 | 19.6 | 3 | 162807 | 12384 | 25-75 |
| AICHI | [17] | [18] | Asia | Japan, Aichi | Civil servants | M+F | 2002 | 9.0 | 3 | 3338 | 225 | 35-66 |
| AIZAWA | [19] |  | Asia | Japan, Matsumoto | Participants from hospital (not otherwise defined) | M+F | 2005 | 4.9 | 2 | 4159 | 279 | Any |
| ALEIN | [20] |  | Asia | Taiwan (China), A-Lein | Persons undergoing community wide screening for hepatitis | M+F | 1996-1997 | 8.0 | 2 | 3539 | 423 | 40-69 |
| ALSWH | [21] |  | Oceania | Australia | General population | F | 1998 | 12.0 | 1 | 12367 | 871 | 47-52 |
| ANSAN | [22] | [23, 24] | Asia | South Korea, Ansun and Ansan | Community based | M+F | 2001-2002 | 4.0 | 2 | 4041 | 329 | 40-69 |
| ARIC | [25] | [26] | North America | United States, North Carolina, Mississippi, Maryland | Probability sample from 4 US communities with exclusive sampling of African Americans in one of the four sites, Black or White | M+F | 1987-1989 | 9.0 | 3 | 10892 | 1254 | 45-64 |
| ASAN | [27] |  | Asia | South Korea, Asan | Attending voluntary medical check-ups | M+F | 2000 | 5.0 | 2 | 5372 | 234 | 20-79 |
| ATTICA | [28] |  | Europe | Greece, Athens | General population | M+F | 2001-2002 | 10.0 | 2 | 1485 | 191 | 18-89 |
| Ausdiab | [29] |  | Oceania | Australia | General population | M+F | 1990-2000 | 5.0 | 2 | 5842 | 244 | 25+ |
| BEDFORD | [30] |  | Europe | England, Bedford | Borderline diabetics with a 2h fasting glucose of 6.7-11.1 mmol/l | M+F | 1962-1964 | 10.0 | 2 | 241 | 36 | 18+ |
| BIP | [31] |  | Asia | Israel | Subjects with impaired functional capacity (New York Heart Association class II and III) | M+F | 1990-1993 | 6.2 | 2 | 630 | 98 | 45-74 |
| BMES | [32] |  | Oceania | Australia, West of Sydney | Non institutionalised residents | M+F | 1992-1994 | 10.0 | 3 | 2123 | 165 | 49+ |
| BOGALUSA | [33] |  | North America | United States, Bogalusa | General population | M+F | 1973-2010 | 9.1 | 2 | 7725 | 176 | <18 |
| BOTNIA | [9] | [34] | Europe | Finland, Botnia | Family members of diabetics | M+F | 1990 | 7.6 | 2 | 2770 | 138 | Any |
| BRHS | [35] |  | Europe | Britain | General population | M | 1978-1980 | 16.8 | 3 | 7124 | 290 | 40-59 |
| BRUNECK | [36] |  | Europe | Italy, Bruneck | General population, White | M+F | 1990 | 10.0 | 2 | 837 | 64 | 40-79 |
| BURKE | [37] |  | Oceania | Australia Kimberley | General population, Aboriginal | M+F | 1988-1989 | 12.9 | 2 | 493 | 104 | 15-88 |
| BWHS | [38] |  | North America | United States | African American subscribers to magazine targeted at black women | F | 1995 | 16.0 | 3 | 43003 | 4387 | 21-69 |
| CASSAN | [39] |  | North America | United States | Majority were veterans, 98% Caucasian | M | 1963 | 18.0 | 2 | 1972 | 226 | 20-80 |
| CCHS | [40] |  | North America | United States, Cleveland | General population | M+F | 2008 | 5.0 | 2 | 5084 | 872 | 18+ |
| CDCdeC | [41] |  | Europe | Spain, Canaries | General population | M+F | 2000-2005 | 3.5 | 3 | 5521 | 146 | 18-75 |
| CEHSC | [42] |  | Asia | Hong Kong (China) | General population volunteers | M+F | 1998-2001 | 9.8 | 2 | 53905 | 806 | 65+ |
| CKB | [43] |  | Asia | China | General population | M+F | 2004-2008 | 7.2 | 2 | 461211 | 8784 | 30-79 |
| CoLaus | [44] |  | Europe | Switzerland, Lausanne | General population | M+F | 2003-2006 | 5.5 | 2 | 3166 | 47 | 35-75 |
| CPSI | [45] |  | North America | United States | General Population | M+F | 1959-1960 | 12.0 | 3 | 709827 | 25397 | 30+ |
| CRISPS | [46] |  | Asia | Hong Kong (China) | General population, Chinese | M+F | 2000-2004 | 9.0 | 2 | 1380 | 123 | Any |
| CURES | [47] |  | Asia | India, Chennai | General population | M+F | 2001-2003 | 9.1 | 2 | 1376 | 385 | 20+ |
| DAQING | [48] |  | Asia | China | Care clinic patients with pre-diabetes, part of diabetes prevention intervention | M+F | 1986 | 23.0 | 3 | 568 | 436 | Any |
| DEHGHA | [49] |  | Europe | Netherlands, Ommoord | General population | M+F | 1990-1993 | 10.8 | 2 | 6935 | 645 | 55+ |
| DE-PLAN | [11]  |  | Europe | Spain, Navarra, Reus and Barcelona | Participants in clinical trial on Mediterranean diet, Caucasian | M+F | 2006 | 4.2 | 2 | 552 | 124 | 45-75 |
| DESIR | [50] |  | Europe | France, Western | Volunteers for periodic health checks | M+F | 1998 | 9.0 | 2 | 3817 | 203 | 30-64 |
| DLCS | [51] |  | Europe | Netherlands, Northern | General population, Western Europe | M+F | 2007-2013 | 4.0 | 3 | 72880 | 1056 | 18-90 |
| DNC | [52] |  | Europe | Denmark | Nurses | F | 1993-1999 | 15.3 | 2 | 24174 | 1137 | 44+ |
| DONGFENG | [53] |  | Asia | China, Da Qing | Retired employees | M+F | 2008-2010 | 4.0 | 3 | 17690 | 1390 | Any |
| DWECS | [54] |  | Europe | Denmark | Workers | M+F | 1995-2005 | 5.0 | 2 | 6823 | NA | 30-59 |
| EPIC-IN | [55] |  | Europe | 8 countries7 | Subset of participants in EPIC-InterAct cohort | M+F | 1991 | 11.7 | 3 | 23501 | 10327 | Any |
| ESTHER | [56] |  | Europe | Germany, Saarland | General population | M+F | 2000-2002 | 8.0 | 3 | 7462 | 718 | 50-75 |
| FAGERB | [57] |  | Europe | Sweden, Göteborg | General population, Caucasian | F | 2001-2004 | 5.5 | 2 | 341 | 69 | 64 |
| FINNMARK | [58] |  | Europe | Norway, Finnmark | General population | M+F | 1997-1978 | 12.0 | 2 | 11654 | 162 | 35-52 |
| GLOSTRUP | [59] |  | Europe | Denmark, Glostrup | General population | M | 1982-2001 | 18.9 | 2 | 5350 | 211 | 30-70 |
| GNHIES | [60] |  | Europe | Germany | General population (non institutionalized) | M+F | 1997-1999 | 5.0 | 2 | 3625 | 82 | 18-79 |
| HDNNCDS | [12] |  | Asia | China, Harbin | General population, Chinese | M+F | 2010 | 4.2 | 3 | 7133 | 578 | 20-74 |
| HEALTH2000 | [10] |  | Europe | Finland | General population | M+F | 2000-2001 | 7.0 | 2 | 4110 | 81 | 40-79 |
| HEINZN | [61] | [62] | Europe | Germany, Western | General population | M+F | 2000-2003 | 5.1 | 3 | 3547 | 319 | 45-75 |
| HENAN | [63] |  | Asia | China, Henan | General population, N Chinese ancestry | M+F | 2007-2008 | 6.0 | 3 | 12272 | 775 | 18+ |
| HIPOP-OHP | [64] |  | Asia | Japan | Employees | M+F | 1999 | 3.4 | 3 | 6498 | 229 | Any |
| HIPPIS1 | [65] |  | Europe | England and Wales | Primary care patients | M+F | 1993-2008 | 8.0 | 2 | 2540753 | 78081 | 25-79 |
| HIPPIS2 | [66] |  | Europe | England | Primary care patients | M+F | 2005-2016 | 3.9 | 2 | 8186705 | 178314 | 25-84 |
| HISAYAMA | [67] |  | Asia | Japan, Hisayama | General population | M+F | 1988 | 11.8 | 2 | 1935 | 286 | 40-79 |
| HPFUS | [68] |  | North America | United States | Health professionals | M | 1986 | 6.0 | 3 | 41810 | 509 | 40-75 |
| HPHS | [12] |  | Asia | China, Harbin | General population, Chinese | M+F | 2008 | 4.2 | 3 | 3350 | 244 | 20-74 |
| HUNT | [69] |  | Europe | Norway, Nord-Trøndelag | General population | M+F | 1984-1997 | 11.0 | 3 | 90819 | 1860 | 20+ |
| ICARIA | [70] |  | Europe | Spain | Spanish workers | M+F | 2004-2007 | 4.1 | 3 | 380366 | 9960 | 18-65 |
| ICS | [71] |  | Asia | Iran, Isfahan, Arak and Najafabad | General population | M+F | 2001 | 7.0 | 2 | 2980 | 389 | 35+ |
| IPC | [72] |  | Europe | France, Paris | Workers and those seeking employment who had undergone 2 health checks | M+F | 1998-2010 | 5.3 | 2 | 22567 | 527 | 18+ |
| IRAS | [73] |  | North America | United States, 4 areas8 | General population | M+F | 1992-1993 | 5.0 | 2 | 906 | 148 | 40-69 |
| IWHS | [74] |  | North America | United States, Iowa | Community based | F | 1986 | 13.2 | 1 | 36839 | 3281 | 55-69 |
| JACC | [75] |  | Asia | Japan | Community based | M+F | 1988-1990 | 5.0 | 1 | 16160 | 396 | 40-79 |
| J-ECOH | [76] | [77] | Asia | Japan | Employees | M+F | 2008-2010 | 3.9 | 2 | 53930 | 2441 | 15-83 |
| JHS | [78] |  | North America | United States, Mississippi | General population, Black | M+F | 2000-2004 | 8.0 | 2 | 2991 | 479 | 21-84 |
| JPHC | [79] |  | Asia | Japan | General population | M+F | 1990 | 10.0 | 1 | 28893 | 1183 | 40-59 |
| JPHC2 | [80] |  | Asia | Japan | General population | M+F | 1995-1998 | 5.0 | 1 | 59834 | 1100 | 45-74 |
| KANGBUK | [81] |  | Asia | South Korea, Seoul | Individuals undergoing health screening | M+F | 2002 | 5.6 | 3 | 174314 | 5544 | 18+ |
| KAWAHA | [82] |  | Asia | Japan, Kitakyushu City | City workers | M+F | 2008 | 3.7 | 2 | 52781 | 4369 | 20-89 |
| KAWAKA | [83] |  | Asia | Japan, electrical company | Employees of large electrical company | M | 1984 | 8.0 | 2 | 2312 | 41 | 18-53 |
| KMIC | [84] |  | Asia | South Korea | Government and school employees | M | 1990-1986 | 8.0 | 2 | 27635 | 1170 | 35-44 |
| KoGES-K | [85] | [86] | Asia | South Korea, Kangwha | Community based | M+F | 2006-2011 | 4.0 | 2 | 2079 | 142 | 40+ |
| KORA F4/FF4 | [87] |  | Europe | Germany, Augsburg | General population | M+F | 2006-2008 | 7.0 | 2 | 504 | 76 | 62-81 |
| KORA S4/F4 | [88] |  | Europe | Germany, Augsburg | General population | M+F | 1999-2001 | 7.0 | 2 | 887 | 93 | 55-74 |
| KPNW | [89] |  | North America | United States, Portland | Health care members | M+F | 1997-2000 | 6.8 | 2 | 46578 | 1854 | 40+ |
| LEICESTER | [90] |  | Europe | England, Leicester | With clinical diagnosis of polycystic ovary syndrome | F | 1988-2009 | 5.2 | 2 | 2164 | 138 | 16-79 |
| LIETO | [91] |  | Europe | Finland, Leito | General population | M | 1998-1999 | 9.0 | 2 | 430 | 30 | 64+ |
| LINDBE | [92] |  | Europe | Denmark, Copenhagen | General population | M+F | 2001-2003 | 8.5 | 2 | 5349 | 136 | 20-94 |
| LLP | [93] |  | Europe | England, Liverpool | General population | M+F | 1998-2008 | 10.0 | 2 | 8753 | 763 | 45-79 |
| MAILES | [94] |  | Oceania | Australia, Adelaide | General population | M | 2002-2006 | 4.9 | 3 | 1597 | 232 | 35-80 |
| MANSON | [95] |  | North America | United States | Physicians in randomized trial | M | 1982 | 12.0 | 1 | 21068 | 770 | 40-84 |
| MECC | [96] |  | North America | United States, Hawaii and California | General population, African American and Latino | M+F | 1993-1996 | 14.0 | 3 | 48995 | 15833 | 50-75 |
| MECH | [97] |  | North America | United States, Hawaii | General population, Caucasian, Hawaiian, Japanese, American | M+F | 1993-1996 | 12.1 | 3 | 74970 | 8559 | 45-75 |
| MESA | [98] | [99] | North America | United States, 6 states9 | General population, White, Black, Hispanic or Chinese | M+F | 2000-2002 | 10.2 | 2 | 5931 | 359 | 45-84 |
| MFH | [10] |  | Europe | Finland | General population | M+F | 1978-1980 | 10.0 | 2 | 4517 | 145 | 40-79 |
| MJH | [100] |  | Asia | Taiwan (China) | Paid members of private health screening program, Chinese | M+F | 2001-2014 | 6.7 | 3 | 147908 | 4781 | 18+ |
| MONICAG | [101] |  | Europe | Germany, Augsburg | General population | M+F | 1984-1995 | 12.5 | 3 | 10892 | 672 | 25-74 |
| MONICAS | [102] |  | Europe | Sweden, Northern | General population | M | 1986-1994 | 8.7 | 3 | 1275 | 27 | 25-74 |
| MORIMO | [103] | [104] | Asia | Japan, Nagano prefecture | Volunteers in Nagano Prefecture | M+F | 1990-1992 | 10.1 | 3 | 5872 | 595 | 40-69 |
| MOZAFF | [105] |  | North America | United States, 4 states10 | Ambulatory, noninstitutionalized subjects | M+F | 1989-1992 | 10.0 | 2 | 4883 | 337 | 65+ |
| MPBB | [106] |  | North America | United States, Michigan | Subjects who had injected food contaminated with polybrominated biphenyls, 99.8% White | M+F | 1976 | 25.0 | 3 | 1384 | 180 | 20+ |
| MPP | [9] |  | Europe | Sweden, Malmo | General population | M+F | 1974-1992 | 24.8 | 2 | 16061 | 2063 | Any |
| MUTUAL | [107] |  | Asia | Japan | Civil servants | M+F | 2000 | 6.5 | 2 | 5848 | 287 | 30-59 |
| MYHUS | [108] |  | Asia | Japan | Employees | M+F | 2004 | 5.0 | 3 | 13700 | 408 | 36-55 |
| NAGALA | [109] | [110] | Asia | Japan, Gifu | Subjects receiving medical check-ups | M+F | 2004-2015 | 5.1 | 3 | 17810 | 804 | Any |
| NAGAYA | [111] |  | Asia | Japan, Nagoya | Volunteer attendants of annual health check ups | M | 1988-1990 | 7.4 | 3 | 16829 | 869 | 30-59 |
| NAKANI | [112] |  | Asia | Japan, Osaka | Employees | M | 1994 | 5.0 | 2 | 1266 | 54 | 35-59 |
| NCDS | [113] |  | Europe | Britain | Birth cohort from March 1958 | M+F | 1974 | 17.0 | 1 | 4945 | 28 | 16 |
| NHANES | [114] |  | North America | United States | General population | M+F | 1971-1975 | 18.0 | 3 | 4830 | 443 | 25-74 |
| NHIC | [115] |  | Asia | South Korea | Recipients of biennial medical check-ups | M+F | 1992-1995 | 14.0 | 2 | 1236443 | 89422 | 30-95 |
| NHIS-HEALS | [116] |  | Asia | South Korea | Recipients of national health screen test | M+F | 2002-2003 | 10.8 | 2 | 359349 | 37678 | 40-79 |
| NHIS-NCS | [117] |  | Asia | South Korea | Nationally representative | M+F | 2002 | 6.8 | 2 | 51405 | 2749 | 20+ |
| NHS | [118] |  | North America | United States | Registered Nurses | F | 1976-1982 | 24.0 | 3 | 100526 | 5392 | 30-55 |
| NHSII | [13] |  | North America | United States | Registered Nurses | F | 1989-1991 | 23.0 | 3 | 88086 | 5441 | 25-42 |
| NIH -AARP | [119] |  | North America | United States, 6 states11  | General population | M+F | 1995-1996 | 11.0 | 1 | 207479 | 18000 | 50-71 |
| NOMAS | [120] |  | North America | United States, North Manhattan | General population, White, Black or Hispanic | M+F | 1993-2001 | 11.0 | 3 | 2430 | 449 | 40+ |
| NOVAK | [121] |  | Europe | Sweden, Gothenburg | General population (intervention group in ineffective trial) | M | 1970-1973 | 35.0 | 2 | 6828 | 899 | 47-56 |
| OLMSTED | [122] |  | North America | United States, Rochester | General population who also took at least one medication | M+F | 1999-2004 | 6.0 | 2 | 13508 | 1182 | 18+ |
| ONAT | [123] |  | Asia | Turkey | Participants in nationwide survey | M+F | 1997-1998 | 5.9 | 3 | 3385 | 216 | 28+ |
| OSAKA | [124] |  | Asia | Japan, Osaka | General population undergoing basic health check-ups | M+F | 2001 | 4.0 | 2 | 9327 | 171 | 40-74 |
| OSLO | [125] |  | Europe | Norway, Oslo | General population | M | 1972-1973 | 28.0 | 3 | 6382 | 584 | 40-49 |
| OSTENS | [126] |  | Europe | Sweden, Stockholm | General population | M | 1992-1994 | 10.0 | 2 | 2383 | 99 | 35-56 |
| PARK | [127] |  | Asia | South Korea, not known | Undergoing health examinations | M | 2002 | 4.0 | 2 | 1717 | 50 | Any |
| PATJA | [128] |  | Europe | Finland, North Karelia and Kuopio | General population | M+F | 1972-1992 | 21.0 | 2 | 41372 | 2770 | 25-64 |
| PINGLIANG | [129] |  | Asia | China, Ping Liang | General population pre-diabetic at baseline | M+F | 2002-2003 | 10.8 | 2 | 334 | 98 | Any |
| PMMJS | [130] |  | Asia | China, Jiangsu | General population | M+F | 2000-2004 | 5.0 | 2 | 3598 | 160 | 35-74 |
| PREDIMED | [11] |  | Europe | Spain, Navarra, Reus and Barcelona | Participants in clinical trial on Mediterranean diet, Caucasian | M+F | 2003-2009 | 4.8 | 2 | 1381 | 155 | 55-80 |
| PREDIMERC | [131] |  | Europe | Spain, Madrid | General population | M+F | 2007 | 6.4 | 2 | 2048 | 44 | 30-74 |
| PREVEND | [132] |  | Europe | Netherlands, Groningen | General population | M+F | 1997-1998 | 11.4 | 3 | 7953 | 447 | Any |
| REGARDS | [133] |  | North America | United States | General population, Black or White | M+F | 2003-2007 | 9.5 | 2 | 7758 | 891 | 45+ |
| SABE | [134] |  | South America | Brazil, Sào Paulo | General population | M+F | 2000 | 6.0 | 1 | 914 | 72 | 60+ |
| SAIREN | [135] |  | Asia | Japan, Ibaraki-ken | General population undergoing annual health check-ups | M+F | 1993 | 5.0 | 2 | 128141 | 7990 | 40-79 |
| SALSA | [136] |  | North America | United States, Sacramento | General population, Latino | M+F | 1998-1999 | 10.0 | 3 | 782 | 144 | 60+ |
| SAMSUNG | [137] |  | Asia | South Korea, Seoul | Undergoing health examinations, Korean | M | 2006 | 6.0 | 3 | 1774 | 180 | 20+ |
| SAPALDIA | [138] |  | Europe | Switzerland | General population | M+F | 2002 | 8.3 | 3 | 2631 | 110 | 18+ |
| SAWADA | [139] |  | Asia | Japan, Tokyo | Employees of Tokyo Gas Company | M | 1985 | 14.0 | 3 | 4745 | 280 | 20-41 |
| SAX45 | [140] |  | Oceania | Australia, New South Wales | General population | M+F | 2006-2008 | 3.4 | 1 | 54997 | 888 | 45+ |
| SCCS | [14] |  | North America | United States, Southern | General population, Black or White | M+F | 2002-2009 | 4.5 | 1 | 35892 | 3439 | 40-79 |
| SCCS2 | [14] |  | North America | United States, Southern | General population, Black or White | M+F | 2012l | 3.0 | 1 | 20712 | 1708 | 43-82 |
| SHFS | [141] |  | North America | United States, 4 states13 | Members of multiplex families, American Indians | M+F | 2001-2003 | 5.5 | 2 | 431 | 133 | 14+ |
| SHIP | [142] |  | Europe | Germany, Augsburg | Caucasian German citizens | M+F | 1997-2001 | 11.1 | 2 | 2034 | 206 | 20-81 |
| SMHS | [143] |  | Asia | China, Shanghai | General population | M | 2002-2006 | 5.4 | 3 | 51464 | 1304 | 40-74 |
| STILLW | [144] |  | Europe | Finland | Employees of Finnish Company | M | 1986 | 17.0 | 2 | 5827 | 313 | 18-65 |
| STRAND | [145] |  | Europe | Finland, Helsinki | Volunteer executives and businessmen | M | 1974-1975 | 20.0 | 3 | 1802 | 94 | 40-56 |
| STRING | [146] | [147] | Europe | England, London | Civil service employees | M+F | 1985-2002 | 23.7 | 2 | 8270 | 1286 | 50 |
| SUGIMO | [148] |  | Asia | Japan, Tokyo | Participants in MHTS | M+F | 1976 | 16.0 | 2 | 2573 | 296 | 18-69 |
| SULAWESI | [149] |  | Asia | Indonesia, South Sulawesi | Three tribes | M+F | 2013 | 3.0 | 2 | 182 | 58 | 16+ |
| SWAN | [150] |  | North America | United States, Michigan | Participants in study of menopause transition, Black or White | F | 1996 | 16.0 | 3 | 424 | 157 | 42-52 |
| TCS | [151] |  | Asia | Thailand | Students at Sukothai Thammithirat Open University | M+F | 2005 | 8.0 | 1 | 39507 | 698 | 15-88 |
| TERATA | [152] |  | Asia | Japan, Chiba | Steelworkers | M | 2002 | 8.0 | 2 | 8423 | 464 | Any |
| TLSA | [153] |  | Asia | Taiwan (China), Non-aboriginal areas | Participants in ongoing survey on aging, Taiwanese | M+F | 1999 | 4.0 | 1 | 2995 | 277 | 53+ |
| TOPICS6 | [154] |  | Asia | Japan, Toranomon | Government employees and some general population | M+F | 1997-2002 | 5.0 | 3 | 7654 | 289 | 40-75 |
| TROMSO | [155] |  | Europe | Norway, Tromsø | General population | M+F | 1994-1995 | 10.8 | 3 | 26168 | 522 | 25-98 |
| UCHIMO | [156] |  | Asia | Japan, Osaka | Employees of large company | M | 1981-1991 | 10.0 | 2 | 6250 | 450 | 35-60 |
| VETERAN | [157] |  | North America | United States | Veterans | M+F | 2002-2003 | 4.0 | 2 | 239057 | 33453 | 18-99 |
| VIP | [158] |  | Europe | Sweden, Västerbotten County | General population | M+F | 1990-2012 | 9.9 | 3 | 32120 | 2211 | 35-55 |
| WHI | [159] |  | North America | United States | Postmenopausal women in a clinical trial or an observational study | F | 1993-1998 | 11.0 | 1 | 135906 | 15076 | 50-79 |
| YOUNGF | [160] |  | Europe | Finland | Population based | M+F | 1980 | 24.0 | 3 | 2298 | 79 | 3-18 |
| ZUTPHEN | [161] |  | Europe | Netherlands, Zutphen | General population | M | 1960 | 25.0 | 2 | 841 | 58 | 40-59 |

1Where relevant, characteristics are shown for the main reference. 2If location not stated, then national. 3All races are included unless stated otherwise. 4NA means not available. Some studies provided results for more than one follow-up time. Here the longest follow-up is indicated. The follow-up times are presented as means, medians or averages to various numbers of decimal places. The values shown are the best estimate available. 51 = self-report only; 2 = medical records only; 3 = both. 6Studies HPFUS, NHS and NHSII. 7France, Italy, Spain, United Kingdom, Netherlands, Germany, Sweden and Denmark. 8Los Angeles, Oakland, San Antonio and San Juis Valley. 9Maryland, Illinois, North Carolina, California, New York and Minnesota. 10North Carolina, California, Maryland and Pennsylvania. 11California, Florida, Louisiana, New Jersey, North Carolina and Pennsylvania. 12Subset of SCCS who were diabetes free at end of SCCS follow-up. Unclear what the baseline date range of SCCS2 actually was. 13Arizona, North and South Dakota and Oklahoma. M: Male; F: Female.

##### Table 3 Meta-analysis random effect relative risks for current smoking

|  |  |  |
| --- | --- | --- |
| **Grouping1** | **Current *vs* never smoking** | **Current *vs* non-smoking** |
| ***n*2** | **RR (95%CI)** | ***P*** | ***n*** | **RR (95%CI)** | ***P*** |
| Overall |  | 99 | 1.33 (1.28-1.38) | *P* < 0.001, *P* < 0.05 | 156 | 1.28 (1.24-1.32) | *P* < 0.001, *P* < 0.05 |
| Sex | Female | 25 | 1.30 (1.23-1.37) |  | 31 | 1.26 (1.21-1.31) |  |
| Male | 36 | 1.40 (1.32-1.49) |  | 47 | 1.30 (1.24-1.36) |  |
| Combined | 38 | 1.28 (1.18-1.39) | NS3 | 78 | 1.26 (1.18-1.34) | NS |
| Continent | Asia | 44 | 1.36 (1.30-1.43) |  | 57 | 1.36 (1.29-1.43) |  |
| Europe | 32 | 1.34 (1.27-1.42) |  | 60 | 1.25 (1.20-1.30) |  |
| North and South America | 19 | 1.27 (1.18-1.37) |  | 34 | 1.18 (1.12-1.25) |  |
| Oceania | 4 | 1.05 (0.68-1.62) | NS | 5 | 1.54 (1.28-1.85) | *P* < 0.001 |
| Publication year | Up to 2005 | 13 | 1.41 (1.27-1.56) |  | 23 | 1.24 (1.16-1.33) |  |
| 2005-2014 | 47 | 1.36 (1.30-1.43) |  | 66 | 1.31 (1.27-1.35) |  |
| 2015 or later | 39 | 1.27 (1.20-1.35) | NS | 67 | 1.23 (1.17-1.30) | NS |
| Basis of diagnosis | Self-report only | 12 | 1.32 (1.25-1.40) |  | 17 | 1.34 (1.25-1.44) |  |
| Medical records only | 49 | 1.32 (1.25-1.38) |  | 86 | 1.29 (1.23-1.34) |  |
| Both | 38 | 1.36 (1.27-1.46) | NS | 53 | 1.24 (1.17-1.32) | NS |
| Population | General | 93 | 1.32 (1.28-1.37) |  | 147 | 1.28 (1.24-1.32) |  |
| Pre-diabetics only | 2 | 3.29 (1.51-7.21) |  | 3 | 1.23 (0.79-1.90) |  |
| Pre-diabetics excluded | 4 | 1.61 (1.30-1.99) | *P* < 0.05 | 6 | 1.38 (1.15-1.67) | NS |
| Number of adjustment factors | 0 | 17 | 1.15 (1.00-1.33) |  | 33 | 1.19 (1.08-1.31) |  |
| 1 to 5 | 18 | 1.36 (1.25-1.47) |  | 30 | 1.38 (1.27-1.51) |  |
| 6 to 10 | 43 | 1.40 (1.32-1.48) |  | 64 | 1.29 (1.25-1.33) |  |
| 11 or more | 21 | 1.28 (1.20-1.37) | *P* < 0.05 | 29 | 1.22 (1.15-1.30) | *P* < 0.1 |
| Cohort size | < 5000 | 35 | 1.36 (1.19-1.56) |  | 58 | 1.31 (1.20-1.42) |  |
| 5000 to 20000 | 20 | 1.38 (1.25-1.53) |  | 43 | 1.24 (1.17-1.32) |  |
| > 20000 | 44 | 1.32 (1.26-1.37) | NS | 55 | 1.29 (1.24-1.35) | NS |
| Number of type 2 diabetes cases | < 500 | 44 | 1.37 (1.23-1.52) |  | 78 | 1.27 (1.19-1.35) |  |
| 500-999 | 18 | 1.50 (1.34-1.67) |  | 24 | 1.40 (1.27-1.55) |  |
| 1000-2000 | 10 | 1.26 (1.15-1.38) |  | 17 | 1.20 (1.11-1.30) |  |
| 2001+ | 27 | 1.29 (1.22-1.35) | *P* < 0.1 | 37 | 1.26 (1.20-1.33) | NS |
| Highest age at baseline | < 60 | 13 | 1.36 (1.23-1.51) |  | 22 | 1.24 (1.16-1.32) |  |
| 60-74 | 27 | 1.44 (1.32-1.56) |  | 38 | 1.36 (1.27-1.45) |  |
| 75+ | 59 | 1.29 (1.24-1.35) | *P* < 0.1 | 96 | 1.26 (1.21-1.31) | NS |
| Length of follow-up (yr) | < 5 | 14 | 1.27 (1.19-1.35) |  | 25 | 1.24 (1.15-1.34) |  |
| 5-10 | 55 | 1.38 (1.30-1.47) |  | 81 | 1.34 (1.28-1.40) |  |
| > 10 | 30 | 1.31 (1.22-1.39) | NS | 50 | 1.22 (1.17-1.28) | *P* < 0.05 |
| Definition of smoking | Cigarette | 47 | 1.32 (1.27-1.38) |  | 63 | 1.25 (1.21-1.29) |  |
| Smoking | 50 | 1.36 (1.26-1.46) |  | 89 | 1.30 (1.23-1.37) |  |
| Tobacco | 2 | 1.10 (0.94-1.29) | *P* < 0.1 | 4 | 1.16 (1.06-1.27) | *P* < 0.1 |
| Adjusted for age | No | 20 | 1.17 (1.04-1.32) |  | 41 | 1.22 (1.12-1.33) |  |
| Yes | 79 | 1.35 (1.31-1.41) | *P* < 0.05 | 115 | 1.29 (1.25-1.33) | NS |
| Adjusted for sex | No  | 72 | 1.35 (1.29-1.41) |  | 107 | 1.27 (1.23-1.32) |  |
| Yes | 27 | 1.29 (1.20-1.39) | NS | 49 | 1.29 (1.20-1.38) | NS |
| Adjusted for BMI | No | 29 | 1.24 (1.11-1.38) |  | 55 | 1.22 (1.13-1.32) |  |
| Yes | 70 | 1.35 (1.30-1.41) | NS | 101 | 1.30 (1.26-1.34) | NS |
| Adjusted for physical activity | No | 41 | 1.27 (1.20-1.35) |  | 87 | 1.27 (1.21-1.33) |  |
| Yes | 58 | 1.36 (1.30-1.43) | *P* < 0.1 | 69 | 1.28 (1.23-1.33) | NS |
| Adjusted for alcohol consumption | No | 42 | 1.26 (1.19-1.34) |  | 87 | 1.26 (1.20-1.32) |  |
| Yes | 57 | 1.37 (1.31-1.43) | *P* < 0.05 | 69 | 1.29 (1.25-1.33) | NS |
| Adjusted for family history of diabetes - | No | 61 | 1.28 (1.22-1.35) |  | 99 | 1.23 (1.17-1.29) |  |
| Yes | 38 | 1.41 (1.33-1.49) | *P* < 0.05 | 57 | 1.34 (1.29-1.40) | *P* < 0.01 |
| Adjusted for education | No | 63 | 1.37 (1.31-1.44) |  | 115 | 1.29 (1.24-1.35) |  |
| Yes | 36 | 1.28 (1.21-1.34) | *P* < 0.05 | 41 | 1.23 (1.18-1.28) | *P* < 0.1 |
| Adjusted for diet | No | 74 | 1.35 (1.29-1.41) |  | 126 | 1.29 (1.24-1.34) |  |
| Yes | 25 | 1.30 (1.22-1.38) | NS | 30 | 1.23 (1.18-1.28) | *P* < 0.1 |
| Adjusted for blood pressure | No | 53 | 1.31 (1.24-1.40) |  | 88 | 1.27 (1.21-1.34) |  |
| Yes | 46 | 1.35 (1.29-1.41) | NS | 68 | 1.28 (1.24-1.33) | NS |
| Adjusted for cholesterol | No | 72 | 1.30 (1.25-1.35) |  | 115 | 1.26 (1.22-1.31) |  |
| Yes | 27 | 1.40 (1.32-1.48) | *P* < 0.05 | 41 | 1.32 (1.25-1.39) | NS |
| Adjusted for glucose | No | 79 | 1.30 (1.25-1.35) |  | 116 | 1.26 (1.22-1.31) |  |
| Yes | 20 | 1.44 (1.35-1.54) | *P* < 0.01 | 40 | 1.34 (1.27-1.41) | NS |
| Adjusted for triglycerides | No | 80 | 1.30 (1.25-1.36) |  | 124 | 1.27 (1.22-1.31) |  |
| Yes | 19 | 1.45 (1.33-1.58) | *P* < 0.05 | 32 | 1.34 (1.24-1.44) | NS |
| Adjusted for waist circumference | No | 82 | 1.34 (1.29-1.40) |  | 136 | 1.28 (1.24-1.32) |  |
| Yes | 17 | 1.29 (1.19-1.41) | NS | 20 | 1.25 (1.16-1.35) | NS |
| Adjusted for any other factors | No | 37 | 1.30 (1.19-1.42) |  | 62 | 1.28 (1.18-1.38) |  |
| Yes | 62 | 1.34 (1.29-1.40) | NS | 94 | 1.27 (1.23-1.30) | NS |

1For sex, publication year, basis of diagnosis, number of adjustment factors, definition of smoking and age adjusted the grouping relates to characteristics of the relative risk. For other factors it relates to characteristics of the study. 2Number of estimates combined. 3NS means not significant, *P* ≥ 0.1. For the overall analysis, the first *P* value relates to heterogeneity between estimates and the second to publication bias. For the other analyses it relates to a test of heterogeneity between the random-effects estimates at each level. Information on publication bias by level of each factor studied is given in Supplementary Files 2 and 4. NS: Not significant; CI: Confidence interval; RR: Relative risk.

##### Table 4 Dose-response analyses for current smoking

|  |  |  |
| --- | --- | --- |
| **Grouping1** | **Current *vs* never smoking** | **Current *vs* non-smoking** |
| ***n*2** | **RR (95%CI)** | ***n*** | **RR (95%CI)** |
| Using key values: |  |  |  |  |
| About 10 cigs/d | 13 | 1.10 (1.03-1.18) | 13 | 1.04 (0.98-1.10) |
| About 20 cigs per d | 13 | 1.31 (1.19-1.44) | 13 | 1.27 (1.16-1.39) |
| About 40 cigs per d | 13 | 1.55 (1.39-1.72) | 13 | 1.54 (1.37-1.72) |
| Low | 23 | 1.17 (1.11-1.23) | 22 | 1.13 (1.07-1.19) |
| Medium | 23 | 1.30 (1.22-1.39) | 22 | 1.26 (1.18-1.34) |
| High | 23 | 1.53 (1.41-1.65) | 22 | 1.48 (1.37-1.60) |
| 1-19 cigs/d | 18 | 1.32 (1.20-1.45) | 17 | 1.20 (1.10-1.30) |
| 20+ | 18 | 1.58 (1.42-1.76) | 17 | 1.44 (1.31-1.59) |

1The key value analysis is based on all studies which provide estimates for each key value (*i.e.*, for a range which included the key value and no other key value). The low/medium/high analysis is based on all studies which provide estimates for exactly three levels. The 1-19, 20+ analysis is based on those studies which reported results only for these two levels. 2Number of estimates combined. CI: Confidence interval; RR: Relative risk.

##### Table 5 Meta-analysis random effects relative risks for former (*vs* never) smoking

|  |  |  |  |
| --- | --- | --- | --- |
| **Grouping1** | ***n*2** | **RR (95%CI)** | ***P*** |
| Overall |  | 100 | 1.13 (1.11-1.16) | *P* < 0.001, *P* < 0.01 |
| Sex | Female | 26 | 1.13 (1.08-1.18) |  |
| Male | 36 | 1.12 (1.08-1.16) |  |
| Combined | 38 | 1.16 (1.09-1.22) | NS**3** |
| Continent | Asia | 44 | 1.16 (1.10-1.22) |  |
| Europe | 32 | 1.13 (1.09-1.18) |  |
| North and South America | 20 | 1.11 (1.07-1.16) |  |
| Oceania | 4 | 1.07 (0.93-1.23) | NS |
| Publication year | Up to 2005 | 13 | 1.13 (1.06-1.21) |  |
| 2005-2014 | 47 | 1.16 (1.11-1.22) |  |
| 2015 or later | 40 | 1.11 (1.08-1.15) | NS |
| Basis of diagnosis | Self-report only | 12 | 1.17 (1.05-1.29) |  |
| Medical records only | 49 | 1.11 (1.08-1.13) |  |
| Both | 39 | 1.16 (1.11-1.22) | *P* < 0.1 |
| Population | General | 94 | 1.13 (1.11-1.16) |  |
| Pre-diabetics only | 2 | 0.97 (0.08-12.64) |  |
| Pre-diabetics excluded | 4 | 1.11 (0.86-1.44) | NS |
| Number of adjustment factors | 0 | 18 | 1.11 (1.01-1.23) |  |
| 1 to 5 | 18 | 1.20 (1.11-1.30) |  |
| 6 to 10 | 42 | 1.12 (1.08-1.17) |  |
| 11 or more | 22 | 1.13 (1.09-1.17) | NS |
| Cohort size | < 5000 | 35 | 1.21 (1.11-1.32) |  |
| 5000 to 20000 | 20 | 1.19 (1.09-1.29) |  |
| > 20000 | 45 | 1.12 (1.09-1.15) | NS |
| Number of type 2 diabetes cases | < 500 | 44 | 1.21 (1.12-1.30) |  |
| 500 to 999 | 18 | 1.11 (1.03-1.20) |  |
| 1000 to 2000 | 10 | 1.26 (1.10-1.45) |  |
| 2001+ | 28 | 1.11 (1.08-1.14) | *P* < 0.1 |
| Highest age at baseline | < 60 | 14 | 1.20 (1.10-1.30) |  |
| 60-74 | 27 | 1.19 (1.10-1.29) |  |
| 75+ | 59 | 1.11 (1.09-1.14) | NS |
| Length of follow-up (yr) | < 5 | 14 | 1.13 (1.08-1.19) |  |
| 5-10 | 55 | 1.16 (1.10-1.23) |  |
| > 10 | 31 | 1.11 (1.08-1.15) | NS |
| Definition of smoking | Cigarette | 48 | 1.12 (1.09-1.15) |  |
| Smoking | 50 | 1.15 (1.10-1.21) |  |
| Tobacco | 2 | 0.95 (0.83-1.08) | *P* < 0.05 |
| Adjusted for age | No | 21 | 1.13 (1.05-1.22) |  |
| Yes | 79 | 1.13 (1.10-1.16) | NS |
| Adjusted for sex | No  | 75 | 1.13 (1.10-1.16) |  |
| Yes | 25 | 1.13 (1.07-1.19) | NS |
| Adjusted for BMI | No | 31 | 1.15 (1.07-1.24) |  |
| Yes | 69 | 1.12 (1.10-1.15) | NS |
| Adjusted for physical activity | No | 41 | 1.15 (1.11-1.20) |  |
| Yes | 59 | 1.12 (1.09-1.16) | NS |
| Adjusted for alcohol consumption | No | 43 | 1.15 (1.10-1.19) |  |
| Yes | 57 | 1.13 (1.09-1.16) | NS |
| Adjusted for family history of diabetes | No | 61 | 1.13 (1.10-1.17) |  |
| Yes | 39 | 1.13 (1.09-1.17) | NS |
| Adjusted for education | No | 65 | 1.16 (1.12-1.19) |  |
| Yes | 35 | 1.09 (1.05-1.14) | *P* < 0.05 |
| Adjusted for diet | No | 75 | 1.14 (1.11-1.17) |  |
| Yes | 25 | 1.12 (1.07-1.16) | NS |
| Adjusted for blood pressure | No | 54 | 1.14 (1.10-1.19) |  |
| Yes | 46 | 1.13 (1.09-1.16) | NS |
| Adjusted for cholesterol | No | 73 | 1.13 (1.10-1.16) |  |
| Yes | 27 | 1.14 (1.08-1.20) | NS |
| Adjusted for glucose | No | 80 | 1.13 (1.10-1.16) |  |
| Yes | 20 | 1.15 (1.07-1.23) | NS |
| Adjusted for triglycerides | No | 81 | 1.12 (1.10-1.15) |  |
| Yes | 19 | 1.17 (1.08-1.27) | NS |
| Adjusted for waist circumference | No | 83 | 1.13 (1.10-1.16) |  |
| Yes | 17 | 1.14 (1.05-1.24) | NS |
| Adjusted for other factors | No | 38 | 1.15 (1.08-1.23) |  |
| Yes | 62 | 1.13 (1.10-1.15) | NS |

1For sex, publication year, basis of diagnosis, number of adjustment factors, definition of smoking and age adjusted the grouping relates to characteristics of the RR. For other factors it relates to characteristics of the study. 2Number of estimates combined. 3NS means not significant, *P* ≥ 0.1. For the overall analysis, the first *P* value relates to heterogeneity between estimates and the second to publication bias. For the other analyses it relates to a test of heterogeneity between the random-effects estimates at each level. Information on publication bias by level of each factor studied is given in Supplementary File 6. CI: Confidence interval; RR: Relative risk; NS: Not significant; BMI: Body mass index.

##### Table 6 Dose-response analyses for former *vs* never smoking (years quit)

| **Grouping1** | ***n*2** | **RR (95%CI)** |
| --- | --- | --- |
| Using key values: | About 3 yr quit | 8 | 1.39 (1.21-1.60) |
| About 7 yr quit | 8 | 1.17 (1.07-1.27) |
| About 12 yr quit | 8 | 1.11 (1.01-1.22) |
| Shortest |  | 14 | 1.46 (1.31-1.63) |
| Longest |  | 14 | 1.13 (1.01-1.27) |

1The key value analysis is based on all studies which provide estimates for each key value (*i.e.*, for a range which included the key value and no other key value). The shortest/longest analysis is based on all studies which provide estimates by years quit. 2Number of estimates combined. CI: Confidence interval; RR: Relative risk.

##### Table 7 Meta-analysis random effects relative risks for ever (*vs* never) smoking

|  |  |  |  |
| --- | --- | --- | --- |
| **Grouping1** | ***n*2** | **RR (95%CI)** | ***P*** |
| Overall |  | 100 | 1.25 (1.21-1.28) | *P* < 0.001, *P* < 0.01 |
| Sex | Female | 24 | 1.25 (1.18-1.31) |  |
| Male | 36 | 1.25 (0.20-1.31) |  |
| Combined | 40 | 1.22 (1.14-1.31) | *P* < 0.05 |
| Continent | Asia | 41 | 1.30 (1.25-1.36) |  |
| Europe | 36 | 1.21 (1.17-1.26) |  |
| North and South America | 20 | 1.19 (1.13-1.26) |  |
| Oceania | 3 | 0.87 (0.48-1.57) | *P* < 0.05 |
| Publication year | Up to 2005 | 13 | 1.25 (1.16-1.34) |  |
| 2005-2014 | 47 | 1.26 (1.20-1.33) |  |
| 2015 or later | 40 | 1.23 (1.18-1.28) | NS**c** |
| Basis of diagnosis | Self-report only | 10 | 1.35 (1.17-1.56) |  |
| Medical records only | 51 | 1.22 (1.18-1.27) |  |
| Both | 39 | 1.26 (1.19-1.33) | NS |
| Population | General | 95 | 1.24 (1.21-1.28) |  |
| Pre-diabetics only | 1 | 3.30 (1.24-8.77) |  |
| Pre-diabetics excluded | 4 | 1.43 (1.17-1.76) | *P* < 0.1 |
| Number of adjustment factors | 0 | 23 | 1.18 (1.06-1.32) |  |
| 1 to 5 | 16 | 1.28 (1.20-1.36) |  |
| 6 to 10 | 40 | 1.24 (1.19-1.30) |  |
| 11 or more | 21 | 1.22 (1.16-1.28) | NS |
| Cohort size | < 5000 | 39 | 1.26 (1.14-1.38) |  |
| 5000 to 20000 | 17 | 1.27 (1.17-1.38) |  |
| > 20000 | 44 | 1.24 (1.20-1.28) | NS |
| Number of type 2 diabetes cases | < 500 | 46 | 1.26 (1.16-1.36) |  |
| 500 to 999 | 17 | 1.32 (1.19-1.47) |  |
| 1000 to 2000 | 9 | 1.28 (1.14-1.43) |  |
| 2001+ | 28 | 1.22 (1.17-1.26) | NS |
| Highest age at baseline | < 60 | 13 | 1.35 (1.23-1.47) |  |
| 60-74 | 27 | 1.32 (1.23-1.41) |  |
| 75+ | 60 | 1.21 (1.17-1.25) | *P* < 0.05 |
| Length of follow-up (yr) | < 5 | 14 | 1.21 (1.15-1.26) |  |
| 5-10 | 56 | 1.29 (1.22-1.35) |  |
| > 10 | 30 | 1.21 (1.15-1.28) | NS |
| Definition of smoking | Cigarette | 48 | 1.22 (1.18-1.26) |  |
| Smoking | 50 | 1.28 (1.20-1.36) |  |
| Tobacco | 2 | 1.09 (0.94-1.25) | *P* < 0.1 |
| Adjusted for age | No | 27 | 1.19 (1.09-1.31) |  |
| Yes | 73 | 1.24 (1.20-1.28) | NS |
| Adjusted for sex | No  | 77 | 1.26 (1.22-1.30) |  |
| Yes | 23 | 1.20 (1.13-1.27) | NS |
| Adjusted for BMI | No | 35 | 1.23 (1.13-1.34) |  |
| Yes | 65 | 1.24 (1.20-1.28) | NS |
| Adjusted for physical activity | No | 43 | 1.26 (1.20-1.32) |  |
| Yes | 57 | 1.24 (1.19-1.29) | NS |
| Adjusted for alcohol consumption | No | 46 | 1.24 (1.19-1.30) |  |
| Yes | 54 | 1.25 (1.20-1.30) | NS |
| Adjusted for family history of diabetes - | No | 62 | 1.22 (1.17-1.27) |  |
| Yes | 38 | 1.28 (1.23-1.33) | NS |
| Adjusted for education | No | 67 | 1.29 (1.24-1.34) |  |
| Yes | 33 | 1.17 (1.12-1.21) | *P* < 0.001 |
| Adjusted for diet | No | 76 | 1.26 (1.22-1.31) |  |
| Yes | 24 | 1.21 (1.15-1.26) | NS |
| Adjusted for blood pressure | No | 57 | 1.25 (1.19-1.32) |  |
| Yes | 43 | 1.23 (1.19-1.27) | NS |
| Adjusted for cholesterol | No | 75 | 1.24 (1.20-1.28) |  |
| Yes | 25 | 1.27 (1.19-1.36) | NS |
| Adjusted for glucose | No | 79 | 1.23 (1.19-1.27) |  |
| Yes | 21 | 1.31 (1.25-1.37) | *P* < 0.05 |
| Adjusted for triglycerides | No | 83 | 1.23 (1.20-1.27) |  |
| Yes | 17 | 1.31 (1.22-1.41) | NS |
| Adjusted for waist circumference | No | 84 | 1.25 (1.21-1.30) |  |
| Yes | 16 | 1.21 (1.12-1.31) | NS |
| Adjusted for other factors | No | 42 | 1.24 (1.15-1.33) |  |
| Yes | 58 | 1.23 (1.20-1.28) | NS |

1For sex, publication year, basis of diagnosis, number of adjustment factors, definition of smoking and age adjusted the grouping relates to characteristics of the relative risk. For other factors it relates to characteristics of the study. 2Number of estimates combined. 3NS means not significant, *P* ≥ 0.1. For the overall analysis, the first *P* value relates to heterogeneity between estimates and the second to publication bias. For the other analyses it relates to a test of heterogeneity between the random-effects estimates at each level. Information on publication bias by level of each factor studied is given in Supplementary File 8. CI: Confidence interval; RR: Relative risk; NS: Not significant.