Published in final edited form as:

Lancet Diabetes Endocrinol. 2015 December ; 3(12): 958–967. doi:10.1016/S2213-8587(15)00316-2.

Relation of active, passive, and quitting smoking with incident diabetes: a meta-analysis and systematic review

An Pan, PhD*, Yeli Wang, MSc*, Mohammad Talaei, MD, MPH, Frank B. Hu, MD, PhD, and Tangchun Wu, MD, PhD

Department of Epidemiology and Biostatistics (Prof A Pan PhD), and Department of Occupational and Environmental Health (Prof T Wu MD PhD), and Key Laboratory of Environment and Health (Prof A Pan PhD and Prof T Wu PhD), Ministry of Education and State Key Laboratory of Environmental Health (Incubating), School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China; Saw Swee Hock School of Public Health (Y Wang and T Talaei), National University of Singapore, Republic of Singapore; Departments of Nutrition (Prof F B Hu MD, PhD) and Epidemiology (Prof F B Hu MD, PhD), Harvard T. H. Chan School of Public Health, Boston, MA, United States; Channing Division of Network Medicine (Prof F B Hu MD, PhD), Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States

Abstract

Background—Cigarette smoking remains the leading avoidable cause of disease burden worldwide, and observational studies have linked various smoking behaviors (active and passive smoking and smoking cessation) with risk of type 2 diabetes. We did a meta-analysis of prospective studies assessing the relation of various smoking behaviors and diabetes risk.

Methods—We systematically searched MEDLINE and EMBASE databases (up to 3 May 2015) with manual searches of the references of retrieved publications and relevant reviews. We included prospective studies that reported risk of type 2 diabetes by baseline smoking status. Relative risks (RRs) and 95% confidence intervals (CIs) were pooled using random-effects models, and subgroup analyses were performed by participant and study characteristics.

Findings—The search yielded 88 prospective studies with nearly 6 million participants and 295446 incident cases. Compared with never smoking, the pooled RR (95% CI) of type 2 diabetes was 1.37 (1.33–1.42) for current smoking (84 studies), 1.14 (1.10–1.18) for former smoking (47 studies), and 1.22 (1.10–1.35) for passive smoking (7 studies). The associations persisted in all subgroups, and a dose-response relation was found for current smoking and diabetes risk: the RRs (95% CIs) were 1.21 (1.10–1.33), 1.34 (1.27–1.41) and 1.57 (1.47–1.66) for light, moderate, and heavy smokers, respectively, compared with never smokers. We estimated that 10.3% in men and

Correspondence to: An Pan, PhD, or Tangchun Wu, MD, PhD, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, 13 Hangkong Rd, Wuhan 430030, Hubei, China; panan@hust.edu.cn, or wut@mails.tjmu.edu.cn.

*The authors contributed equally to the paper.

Contributors: AP conceived the study, did the search, analysed and interpreted the data, and drafted and critically revised the reports. YW and MT screened the references, extracted the data, and critically revised the reports. FBH and TW conceived the study, and critically revised the reports.

Declaration of interests: We declare no competing interests.

2.2% in women of type 2 diabetes cases (approximately 25 million) were attributable to cigarette smoking worldwide if smoking is causally related to diabetes. Compared to never smokers, the pooled RR (95% CI) from 10 studies was 1.54 (1.36-1.74) in new quitters (<5 years), and 1.11 (1.02-1.20) in long-term quitters (≥ 10 years).

Interpretation—Active and passive smoking are associated with significantly increased risks of type 2 diabetes. The risk of diabetes is elevated in new quitters, but decreases substantially as the time since quitting increases.

Keywords

smoking; diabetes mellitus; meta-analysis; cohort studies

Introduction

Despite global effort to fight the tobacco epidemic, cigarette smoking remains the leading avoidable cause of morbidity and mortality, killing nearly 6 million people each year worldwide.¹ Smoking is undoubtedly a key risk factor for cancer, respiratory diseases and cardiovascular disease;² however, the link between smoking and diabetes risk has not been widely acknowledged. A previous meta-analysis³ summarized the association between smoking and diabetes risk from 25 prospective studies published up to 2007. The 2014 US Surgeon General's Report, for the first time, included a section of smoking and diabetes risk and argued for the causal relation between them,² but it did not discuss the relation of passive smoking and smoking cessation with diabetes risk.

Furthermore, growing evidence from epidemiologic studies suggests that passive smoking is also associated with an increased risk of type 2 diabetes.⁴⁻⁶ In addition, several studies reported that diabetes risk was increased in individuals who had recently quit smoking, raising a concern about elevated diabetes risk with smoking cessation.⁷⁻¹⁶ Therefore, quantifying the association between duration since smoking cessation and diabetes risk will provide direct evidence for clinical practice and public health policy.

To provide an up-to-date quantitative estimate of the smoking-diabetes association, we conducted a comprehensive systematic review and meta-analysis of prospective cohort studies to summarize the associations between various smoking behaviors (current and former smoking, passive smoking and smoking cessation) and risk of type 2 diabetes.

Methods

Data sources

We did this systematic review in accordance with the PRISMA and MOOSE guidelines.^{17,18} We conducted a literature search (up to 3 May 2015) of MEDLINE and EMBASE for studies describing the association between cigarette smoking and risk of type 2 diabetes. The search focused on three themes of Medical Subject Headings (MeSH) terms and related exploded versions: smoking or cigarette, diabetes mellitus or glucose metabolism irregularity, and studies with a prospective design. The three themes were combined using the Boolean operator “and.” No restrictions in the search strategy were inserted. The detailed

search strategies are shown in the Supplemental Material. In addition, we searched the reference lists of all included publications and relevant reviews.²⁻⁶

Study selection

Two investigators (Y.W. and M.T.) independently assessed literature eligibility; discrepancies were resolved by consensus, or determined by a third investigator (A.P.). Articles were considered for inclusion in the systematic review if: (1) the authors reported data from an original, peer-reviewed study (e.g., not review articles or meeting abstracts); (2) the study was a prospective study among non-institutionalized adults without diabetes at baseline; and (3) the authors reported risk estimates of type 2 diabetes by smoking status; and (4) studies were published in English. Studies reporting crude associations without any adjustment were excluded. In the case of multiple publications, we included reports with the longest follow-up years or largest incident cases. We evaluated eligible articles first by screening titles or abstracts, followed by full-text reviews.

Data extraction

We extracted the following information using a pre-designed collection form: study characteristics (study name, authors, publication year, journal, study location, follow-up years, and number of participants and incident cases), participants' characteristics (mean age or age range, sex, ethnicity), smoking status (never, past and current smoking, passive smoking, number of cigarettes per day and years since quitting smoking), diabetes outcome assessment methods (self-report, medical record or clinical examination), and analysis strategy (statistical models, covariates included in the models). If the information was unavailable or unclear from a published report, we collected relevant data by corresponding with the authors. Quality assessment was performed using the 9-item Newcastle-Ottawa Scale;¹⁹ validity of exposure and outcome measurements, exclusion of outcome at baseline, selection of non-exposure group, adequacy of follow-up, proportion of lost-to-follow-up, confounding adjustment (2 items), and generalizability to other populations. We added another item whether smoking was a major exposure under study in the article. Overall, the scale awards a maximum of 10 points for study quality with higher score representing higher quality.

Statistical analysis

Separate meta-analyses were conducted to determine the risk of incident diabetes associated with: (1) active smoking (including current and former smoking, smoking intensity); (2) passive smoking; and (3) years since smoking cessation. The relative risk (RR) was used as the common measure of association across studies, and the hazard ratio, incidence density ratio, or odds ratio was considered approximate to RR given the low incidence rate. The RRs were pooled using the DerSimonian and Laird²⁰ inverse-variance-weighted random-effects models, which allowed between-study heterogeneity, and forest plots were produced. Heterogeneity across studies was evaluated by the Cochrane Q statistic (significance level of $P < 0.10$) and the I^2 statistic (higher values representing higher heterogeneity).^{21,22} When substantial heterogeneity was present, the 95% prediction interval was also calculated to account for the uncertainty of the summary estimate and the between-study variation.²³

Moreover, pre-specified meta-regression and stratified analyses were performed as exploratory analyses to evaluate the influences of selected study and participant characteristics on the results. Publication bias was evaluated using the Egger's test and visual inspection of a funnel plot.²⁴ The Duval and Tweedie²⁵ nonparametric trim-and-fill method was used to further assess the possible effect of publication bias.

We also conducted a dose-response analysis of smoking intensity and diabetes risk. Studies have used different categories for the intensity of smoking (e.g., some classified by cigarettes per day, and some used pack-years), thus we re-categorized the frequencies into three groups (light, moderate and heavy smokers) based on the study-specific distributions or classifications. In most studies, light smokers referred to those who smoked <10 cigarettes per day (or <20 pack-years), while heavy smokers referred to those who smoked ≥20 cigarettes per day (or ≥40 pack-years).

In the analysis of smoking cessation and diabetes risk, all studies used never smoking as the reference group and reported RRs associated with categories of years since smoking cessation, which varied across studies. Therefore, we modified the data into three groups: <5 (new quitters), 5-10, and ≥10 years (long-term quitters). Two studies^{11,13} reported results for <3 and 3-5 years since quitting smoking, thus the two categories were combined to <5 years as new quitters using meta-analysis approach. Some studies^{8,12,15} reported more categories for ≥10 years since smoking cessation, and they were combined to ≥10 years as long-term quitters using meta-analysis approach. In one study,⁷ the new quitters were defined as quitting <3 years, and in another study,¹⁰ the long-term quitters were defined as quitting ≥8 years.

We calculated absolute risk differences associated with smoking by multiplying the background incidence rate of diabetes in the general US population²⁶ with (estimated RR-1). Population attributable fraction (PAF) was calculated based on the following equation: $PAF = 100\% \times P_e(RR-1)/(P_e[RR-1]+1)$, where P_e is the prevalence of the smoking in the population and RR was derived from this meta-analysis. All analyses were performed with Stata version 11.2 (Stata Corp, College Station, Texas).

Role of the funding source

The study funders did not contribute to the study design and had no role in data gathering, analysis, or interpretation, or the writing of the report. AP had full access to all the raw data and take final responsibility for the decision to submit for publication.

Results

Literature search

We identified 12598 unique citations from the two databases. After the screening based on the aforementioned criteria and detailed examination, 88 articles were included in the final meta-analysis (Figure 1). The full list of the included publications is shown in the Supplemental Material.

Among these 88 articles, 84 studies focused on active smoking, of which 3 studies also reported results for passive smoking among never smokers and 10 reported results for smoking cessation. Another 4 studies only showed results for passive smoking among never smokers, thus a total of 7 studies were included for the analysis of passive smoking. The characteristics of the included studies are shown in the Appendix Tables 1-3. The study quality assessment is shown in the Appendix Table 4.

Active smoking and risk of incident type 2 diabetes

Characteristics of the studies reporting active smoking and diabetes are shown in the Appendix Table 1. All studies reported results for type 2 diabetes, while some studies²⁷⁻³⁰ used less stringent criteria for diabetes and include those with impaired fasting glucose (≥ 6.1 mmol/L or 110 mg/dL). Smoking status was self-reported in all studies, except in the study by Houston et al,²⁷ where it was validated against serum cotinine level. The sample size ranged from 241 to 2540753 with a total of 5853952 participants and 294081 incident diabetes cases. Of the 84 studies, most were conducted in European countries (n=32), US (n=19), and Japan (n=17), and the others were done in Korea (n=5), mainland China and Taiwan (n=4), Australia (n=3), Israel (n=2), Turkey (n=1), and Iran (n=1). Most studies included both men and women, while 27 studies were conducted exclusively in men and 5 in women. The median follow-up year was 9 (interquartile range 5-9-12-9). The prevalence of current smoking varied across studies. A total of 12 studies reported their results separately by sex, and thus there were 96 comparisons from 84 studies.

The RR (95% CI) comparing active smokers with nonsmokers was 1.37 (1.33-1.42; Appendix Figure 1) from random-effects model, and 1.29 (1.28-1.32) from the fixed-effect model (data not shown). The results were similar when comparing current smoking with never (RR 1.40; 95% CI 1.33-1.47) or non-current smoking (1.35; 1.27-1.42), or comparing ever with never smoking (1.35; 1.16-1.57; Table 1). We also found a dose-response relation of smoking intensity and diabetes risk, and the pooled RRs (95% CI) were 1.21 (1.10-1.33), 1.34 (1.27-1.41) and 1.57 (1.47-1.66) for light, moderate and heavy smokers, respectively, compared with never smokers (Table 1). Similar dose-response patterns were found when using cigarettes per day as the marker for current smoking status, or using pack-years as the marker for cumulative smoking exposures (Figure 2).

A substantial heterogeneity was detected ($I^2=68.6\%$; $p<0.001$), and the RR should be interpreted as the average estimate of the associations between smoking and diabetes risk. Thus, the 95% prediction interval was calculated as 1.11-1.70. We further conducted stratified analysis to explore the heterogeneity, and the increased risk was consistently found in all strata while the heterogeneity remained high (Table 1). The association was slightly stronger in men, when smoking was the main exposure and when diabetes was detected by blood glucose levels, compared to their counterparts. However, no statistically significant differences were found across strata (all p values from meta-regression >0.10).

Furthermore, 47 studies (with 56 comparisons) compared former with never smoking, and the pooled RR was 1.14 (95% CI 1.10-1.18; $I^2=59.7\%$; Table 1 and Appendix Figure 2). Again, the increased risk persisted in all stratified analyses and no significant differences across strata were found.

Passive smoking and risk of incident type 2 diabetes

Characteristics of the studies reporting passive smoking and diabetes risk are shown in Appendix Table 2. Of the seven studies, three^{12,27,36} were also included in the analysis of active smoking and diabetes, and four³⁷⁻⁴⁰ were not. Five studies^{27,36-39} were done in both genders and two^{12,40} were exclusively in females. A total of 156439 participants with 7843 incident diabetes cases were included. Three studies were done in US populations,^{12,27,38} two in Europeans,^{37,40} and two in Asians (Korean and Japanese).^{36,39} Compared with never smokers with no passive smoke exposure, the pooled RR of type 2 diabetes was 1.22 (95% CI 1.10-1.35) in passive smokers with low heterogeneity ($I^2=32.6\%$; $p=0.18$; Appendix Figure 3).

Smoking cessation and risk of incident type 2 diabetes

Among the studies of former smokers, 10 studies reported detailed information of years since quitting smoking. The characteristics of the 10 studies are shown in Appendix Table 3. Five studies^{7,9,11,12,15} were done in US populations, two^{8,16} in European populations, and three^{10,13,14} in Asians (Korean and Japanese). Four studies^{7,8,10,14} were exclusively in men, two^{12,15} were in women only, and four^{9,11,14,16} were in both genders (while three^{9,14,16} of them reported results separately for men and women). Compared with never smokers, the pooled RR (95% CI) was 1.54 (1.36-1.74) in new quitters (<5 years), 1.18 (1.07-1.29) in middle-term quitters (5-9 years), and 1.11 (1.02-1.20) among long-term quitters (≥ 10 years) (Figure 3 and Appendix Figure 4). Interestingly, the RRs in all 10 studies were significant comparing new quitters with never smokers, suggesting that the diabetes risk consistently remained higher in the short term after quitting smoking. When stratified by study population, the increased risk in new quitters was much higher in Asians (RR 2.04; 95% CI 1.50-2.77) compared to Caucasians (RR 1.43; 95% CI 1.26-1.62) (p value from meta-regression = 0.045; Appendix Table 5). In the 10 studies, the pooled RR was 1.47 (95% CI 1.34-1.62) comparing continuous smoking with never smoking (Appendix Table 5).

Assessment of publication bias

Visual inspection of the funnel plot revealed asymmetry for current smoking (Appendix Figure 5A), and the Egger's test was significant ($p<0.001$). The pooled RR was 1.29 (95% CI 1.25-1.34) after performing the trim-and-fill method. Similarly, significant asymmetry in the funnel plot was observed for former smoking ($p=0.001$; Appendix Figure 5B; RR 1.10 using the trim-and-fill method; 95% CI 1.06-1.14). No significant publication bias was observed for passive smoking ($p=0.17$; Appendix Figure 5C).

Absolute risk difference and population attributable fraction

Using data from the 2014 National Diabetes Statistics Report in US adults aged >20 years,²⁶ we estimated that the absolute risk difference of type 2 diabetes associated with smoking was 289 per 100000 individuals per year. The absolute risk difference will be higher in populations with higher incidence rate (e.g., middle-aged and elderly populations). According to the global prevalence of daily smoking from a recent publication⁴¹ and data from the International Diabetes Federation,⁴² our meta-analysis suggested that 10.3% (20.5 million out of 199.2 million) of total diabetes cases in men and 2.2% (4.1 million out of

188.4 million) in women were attributable to active smoking worldwide (Appendix Table 6), if smoking is causally related to diabetes. The PAF calculations should vary in populations with different smoking prevalence, and we used the populations in the United States, United Kingdom, and China as examples in the Appendix Table 5. As shown in the Table, the PAFs were higher in UK (7.3%) and US (4.6%) but smaller in China (0.9%) among women; while in men, the PAFs were much higher in China (15.6%) compared to UK (8.2%) and US (5.5%).

Discussion

Using data from 88 prospective studies of almost 6 million participants, our meta-analysis demonstrated that both active and passive smoking were associated with increased risk of incident type 2 diabetes (RR=1.37 and 1.22, respectively). In addition, the associations persisted across all subgroups stratified by various study and participant's characteristics. Furthermore, although former smokers still had a higher risk compared to never smokers, the increased risk (RR=1.14) was much lower compared to that in current smokers (RR=1.37), supporting the benefits of smoking cessation to reduce diabetes risk. A detailed analysis of years since quitting smoking also revealed that smoking cessation substantially decreased diabetes risk in the long-term despite elevated risk in the new quitters.

Our results are consistent with two previous meta-analyses of active smoking and diabetes risk.^{2,3} The recent US Surgeon General's Report included 46 studies published before 2010, and obtained a pooled RR of 1.37 (95% CI 1.31–1.44).² Since then, many more studies have been published. Our current meta-analysis extended those reports and included a total of 84 studies on active smoking, thus provided the most accurate and comprehensive estimates of smoking and diabetes risk. The study by Willi et al.³ reported that the association varied significantly in some strata, including baseline age, BMI, and follow-up years. However, the number of studies in that analysis was much smaller (n=25) and the statistical power was low. Our current meta-analysis did not reveal substantial differences across study and participant's characteristics; however, significant heterogeneity remained in most subgroups.

Most previous studies have focused on active smoking and risk of type 2 diabetes, and accumulating evidence has suggested that secondhand smoking could also be a concern. Several meta-analyses^{4–6} have recently summarized the data on this topic, but they included only a limited number of cohort studies, and one included cross-sectional studies in the analysis.⁶ A recent analysis⁴³ estimated that over 30% of worldwide non-smokers were exposed to secondhand smoking and it contributed to about 1% of global total mortality and 0.7% of disease burden. However, diabetes was not included in that analysis of disease burden. Taken together, our findings further underscore the importance of adoption and enforcement of smoke-free legislation to reduce the number of people exposed to secondhand smoke.

Similar to other studies that have indicated a causal link between smoking and multiple disease outcomes (cancer, CVD, and mortality),² our results have indicated that smoking is likely to be a causal risk factor for diabetes. In particular, our meta-analysis provides further evidence of dose-response relation (by both current smoking intensity and cumulative

smoking exposure), and more importantly, the substantial benefits related to smoking cessation in the long term. Our pooled estimates showed an increased risk in new quitters compared to never smokers ($RR=1.54$), however, the RR decreased substantially to about 1.18 after 5 years and to 1.11 after 10 years. To the best of our knowledge, this is the first meta-analysis of the association between smoking cessation and diabetes risk. The relation between smoking and body weight is complex: smokers generally have a lower BMI than nonsmokers, while smoking cessation usually leads to weight gain.⁴⁴ A meta-analysis found that smoking cessation is associated with a mean increase of 4.5 kg in body weight after 12 months of abstinence,⁴⁵ and this may be a major barrier for smokers motivated to quit smoking and explains the increased diabetes risk in the short term. However, all the included studies adjusted for baseline BMI in the models, and some studies^{10,13,14} further adjusted for weight gain or used BMI as a time-varying covariate, but the increased risk remained. Oba et al.¹⁴ also stratified the analysis by weight gain status, and reported that the increased risk was observed among male new quitters who gained <3 kg weight during the first 5-year cessation, but not in those who gained ≥ 3 kg. In some studies,^{7,11} the association was slightly attenuated after adjustment for weight gain. Therefore, the short-term diabetes risk associated with smoking cessation is not entirely mediated by weight gain. Some experimental studies found that insulin sensitivity and lipid profiles were improved after short and long-term smoking cessation;⁴⁶⁻⁴⁸ however, the results are not entirely consistent,⁴⁹⁻⁵¹ and a recent large retrospective cohort study in UK primary care database even found deterioration effect in glycemic control that lasted for 3 years after smoking cessation which was independent of weight gain in type 2 diabetic patients.⁵²

The short-term elevated risk in new quitters could also be due to reverse causation because people who try to quit smoking are more likely to have pre-clinical conditions or high cumulative smoking exposures. Unfortunately, none of the studies provided detailed information on the reasons of smoking cessation; therefore, we could not test whether quitters may already have a higher risk for diabetes. However, the characteristics of new quitters were not substantially different from the continuous smokers, including several smoking metrics such as age at smoking initiation, smoking years and number of cigarettes per day at baseline.^{11,13,15} Furthermore, all the studies have extensively controlled for the baseline lifestyle factors and health status (Appendix Table 3); thus, it is unlikely that the results were severely affected by inherent high risk of diabetes in new quitters. Finally, some studies^{11,14,15} reported that the increased risk in new quitters was only seen in long-term heavy smokers before quitting but not in light smokers. Thus, the elevated risk in new quitters might depend on the cumulative smoking exposures prior to quitting. Taken together, the underlying mechanisms of smoking cessation and short-term elevated diabetes risk remain to be elucidated. Nevertheless, smoking cessation has been well documented to reduce the risk of cardiovascular disease^{53,54} and mortality,^{55,56} in both short and long term, and even in diabetic patients.^{53,54} Therefore, the long-term benefits of smoking cessation on diabetes and other health outcomes would greatly offset the short-term elevated risk of diabetes.

Despite large reductions in the prevalence of smoking over the past several decades,⁴¹ smoking remains to be a major public health threat globally.¹ We estimated that 10.3% of diabetes cases in men and 2.2% in women were attributable to current smoking worldwide,

if smoking is a causal risk factor for diabetes. These numbers might be underestimated for several reasons. First, we used the daily smoking prevalence,⁴¹ and the PAFs would be higher if we used the current smoking prevalence from the WHO database.⁵⁷ Second, we did not include exposure to secondhand smoking in the calculation, and the reduction of active smoking would automatically reduce the prevalence of secondhand smoking, which will also translate to beneficial impact on diabetes risk. However, the PAF assumes that no-one starts smoking, and thus it could be overestimated because the risk in current smokers does not return to 1 with long term cessation. Our results are comparable to the recent WHO report,¹ where globally 16% of deaths in men and 7% in women were attributable to smoking, and the Global Burden of Disease Study 2010 that 8.4% of disease burden in men and 3.7% in women were attributable to tobacco smoking (including secondhand smoke).⁵⁸

Several limitations of this meta-analysis should be acknowledged. First, we found a significant heterogeneity across studies for the association between active smoking and diabetes risk, which may result from very large number of included studies, differences in study populations, study quality, analysis strategies, and participant's characteristics. Although moderate to high heterogeneities still existed, the pooled RRs showed consistent positive associations in all subgroups and the prediction interval remained significant. Second, we only included English publications, and unpublished reports are also possible. However, we have tried multiple sources to screen for eligible studies, and the trim-and-fill method suggested that publication bias would not materially alter the associations. In addition, the asymmetry of a funnel plot does not necessarily imply publication bias and the high heterogeneity could also partly be a reason.⁵⁹ Third, residual confounding is still possible given that smoking is commonly related to other unhealthy lifestyle factors (e.g., poor diet, excessive alcohol use, and physical inactivity) and comorbidities.^{60,61} However, no substantial differences were found in studies with and without adjustment for those factors. Nevertheless, the included studies were all observational in nature, and thus causality could not be proven. However, the association is biologically plausible because smoking is associated with central obesity, increases oxidative stress and inflammation, and eventually leads to insulin resistance and hyperglycemia.^{44,62} Fourth, misclassifications existed in the assessment of exposure (self-reported smoking status only at baseline in most studies) and outcome (self-reported or linkage-identified incident diabetes in many studies). We were unable to evaluate the influence of changes in smoking status during follow-up on diabetes risk, while the stratified analysis by outcome assessment suggested a slightly stronger relation with diabetes detected by blood glucose levels. The misclassification was likely to be more substantial in the analysis of passive smoking, and the results might be biased towards null.⁶³ Finally, none of studies directly compared recent quitters with those who continued to smoke in terms of diabetes risk; thus, it is unclear whether short-term smoking cessation could lead to an increased or decreased risk of diabetes compared to continuous smoking.

In conclusion, this meta-analysis has contributed to the growing evidence that both active and passive smoking are significant modifiable factors for risk of type 2 diabetes. Although diabetes risk remains high in the short-term after smoking cessation, the risk decreases substantially in the long run. Given the high prevalence of smoking in many countries and the increasing number of diabetes worldwide, reducing tobacco use should be prioritized as

a key public health strategy to prevent and control global epidemic of diabetes. More efforts are still warranted to implement and enforce the provisions of WHO Framework Convention on Tobacco Control⁶⁴ to reduce cigarette consumption among current smokers. The smoke-free policies can provide protections for non-smokers and may lead to increased successful cessation in smokers. Finally, the mechanisms underlying the short-term increased risk of diabetes in the new quitter need to be further explored, which can help develop targeted pharmaceutical and lifestyle interventions to improve the successful smoking cessation rate and prevent the occurrence of diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

None.

Funding: The project was supported by the National Thousand Talents Program for Distinguished Young Scholars, China (Dr. Pan), NIH grant DK58845 (Dr. Hu), the National 111 Project and the Program for Changjiang Scholars and Innovative Research Team in University by Ministry of Education, China (Dr. Wu).

References

1. World Health Organization. WHO global report: mortality attributable to tobacco 2012. Geneva, Switzerland: World Health Organization; 2013. http://www.who.int/tobacco/publications/surveillance/rep_mortality_attributable/en/ [accessed March 9, 2015]
2. US Department of Health and Human Services. The Health Consequences of Smoking-50 Years of Progress A report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
3. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2007; 298:2654–64. [PubMed: 18073361]
4. Wang Y, Ji J, Liu YJ, Deng X, He QQ. Passive smoking and risk of type 2 diabetes: a meta-analysis of prospective cohort studies. *PLoS One*. 2013; 8:e69915. [PubMed: 23922856]
5. Sun K, Liu D, Wang C, Ren M, Yang C, Yan L. Passive smoke exposure and risk of diabetes: a meta-analysis of prospective studies. *Endocrine*. 2014; 47:421–7. [PubMed: 24532101]
6. Wei X, E M, Yu S. A meta-analysis of passive smoking and risk of developing Type 2 Diabetes Mellitus. *Diabetes Res Clin Pract*. 2015; 107:9–14. [PubMed: 25488377]
7. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ*. 1995; 310:555–9. [PubMed: 7888928]
8. Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. *Diabetes Care*. 2001; 24:1590–5. [PubMed: 11522704]
9. Will JC, Galuska DA, Ford ES, Mokdad A, Calle EE. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int J Epidemiol*. 2001; 30:540–6. [PubMed: 11416080]
10. Hur NW, Kim HC, Nam CM, Jee SH, Lee HC, Suh I. Smoking cessation and risk of type 2 diabetes mellitus: Korea Medical Insurance Corporation Study. *Eur J Cardiovasc Prev Rehabil*. 2007; 14:244–9. [PubMed: 17446803]
11. Yeh HC, Duncan BB, Schmidt MI, Wang NY, Brancati FL. Smoking, smoking cessation, and risk for type 2 diabetes mellitus: a cohort study. *Ann Intern Med*. 2010; 152:10–7. [PubMed: 20048267]

12. Zhang L, Curhan GC, Hu FB, Rimm EB, Forman JP. Association between passive and active smoking and incident type 2 diabetes in women. *Diabetes Care*. 2011; 34:892–7. [PubMed: 21355099]
13. Morimoto A, Ohno Y, Tatsumi Y, et al. Impact of smoking cessation on incidence of diabetes mellitus among overweight or normal-weight Japanese men. *Diabetes Res Clin Pract*. 2012; 96:407–13. [PubMed: 22494491]
14. Oba S, Noda M, Waki K, et al. Smoking cessation increases short-term risk of type 2 diabetes irrespective of weight gain: the Japan Public Health Center-Based Prospective Study. *PLoS One*. 2012; 7:e17061. [PubMed: 22879858]
15. Luo J, Rossouw J, Tong E, et al. Smoking and diabetes: does the increased risk ever go away? *Am J Epidemiol*. 2013; 178:937–45. [PubMed: 23817918]
16. Spijkerman AM, van der AD, Nilsson PM, et al. Smoking and long-term risk of type 2 diabetes: the EPIC-InterAct study in European populations. *Diabetes Care*. 2014; 37:3164–71. [PubMed: 25336749]
17. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000; 283:2008–12. [PubMed: 10789670]
18. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009; 6:e1000097. [PubMed: 19621072]
19. Wells, GA.; Shea, B.; O'Connell, D., et al. [accessed May 1, 2015] The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177–88. [PubMed: 3802833]
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002; 21:1539–58. [PubMed: 12111919]
22. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003; 327:557–60. [PubMed: 12958120]
23. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analysis. *BMJ*. 2011; 342:d549. [PubMed: 21310794]
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997; 315:629–34. [PubMed: 9310563]
25. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000; 56:455–63. [PubMed: 10877304]
26. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta, GA: US Department of Health and Human Services; 2014. <http://www.cdc.gov/diabetes/data/statistics/2014statisticsreport.html> [accessed June 12, 2015]
27. Houston TK, Person SD, Pletcher MJ, Liu K, Iribarren C, Kiefe CI. Active and passive smoking and development of glucose intolerance among young adults in a prospective cohort: CARDIA study. *BMJ*. 2006; 332:1064–9. [PubMed: 16603565]
28. Sugimori H, Miyakawa M, Yoshida K, et al. Health risk assessment for diabetes mellitus based on longitudinal analysis of MHTS database. *J Med Syst*. 1998; 22:27–32. [PubMed: 9554107]
29. Akbaraly TN, Fontbonne A, Favier A, Berr C. Plasma carotenoids and onset of dysglycemia in an elderly population: results of the Epidemiology of Vascular Ageing Study. *Diabetes Care*. 2008; 31:1355–9. [PubMed: 18390802]
30. Fagerberg B, Kellis D, Bergstrom G, Behre CJ. Adiponectin in relation to insulin sensitivity and insulin secretion in the development of type 2 diabetes: a prospective study in 64-year-old women. *J Intern Med*. 2011; 269:636–43. [PubMed: 21198995]
31. Lyssenko V, Almgren P, Anevski D, et al. Predictors of and longitudinal changes in insulin sensitivity and secretion preceding onset of type 2 diabetes. *Diabetes*. 2005; 54:166–74. [PubMed: 15616025]

32. Patja K, Jousilahti P, Hu G, Valle T, Qiao Q, Tuomilehto J. Effects of smoking, obesity and physical activity on the risk of type 2 diabetes in middle-aged Finnish men and women. *J Intern Med.* 2005; 258:356–62. [PubMed: 16164575]
33. Rathmann W, Strassburger K, Heier M, et al. Incidence of Type 2 diabetes in the elderly German population and the effect of clinical and lifestyle risk factors: KORA S4/F4 cohort study. *Diabet Med.* 2009; 26:1212–9. [PubMed: 20002472]
34. Dehghan A, van Hoek M, Sijbrands EJ, Stijnen T, Hofman A, Witteman JC. Risk of type 2 diabetes attributable to C-reactive protein and other risk factors. *Diabetes Care.* 2007; 30:2695–9. [PubMed: 17623828]
35. Steinbrecher A, Morimoto Y, Heak S, et al. The preventable proportion of type 2 diabetes by ethnicity: the multiethnic cohort. *Ann Epidemiol.* 2011; 21:526–35. [PubMed: 21497517]
36. Hayashino Y, Fukuhara S, Okamura T, et al. A prospective study of passive smoking and risk of diabetes in a cohort of workers: the High-Risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) study. *Diabetes Care.* 2008; 31:732–4. [PubMed: 18235051]
37. Kowall B, Rathmann W, Strassburger K, et al. Association of passive and active smoking with incident type 2 diabetes mellitus in the elderly population: the KORA S4/F4 cohort study. *Eur J Epidemiol.* 2010; 25:393–402. [PubMed: 20369275]
38. Hunt KJ, Hansis-Diarte A, Shipman K, Korte JE, Fowler SP, Stern MP. Impact of parental smoking on diabetes, hypertension and the metabolic syndrome in adult men and women in the San Antonio Heart Study. *Diabetologia.* 2006; 49:2291–8. [PubMed: 16896933]
39. Ko KP, Min H, Ahn Y, et al. A prospective study investigating the association between environmental tobacco smoke exposure and the incidence of type 2 diabetes in never smokers. *Ann Epidemiol.* 2011; 21:42–7. [PubMed: 21130368]
40. Lajous M, Tondeur L, Fagherazzi G, de Lauzon-Guillain B, Boutron-Ruault MC, Clavel-Chapelon F. Childhood and adult secondhand smoke and type 2 diabetes in women. *Diabetes Care.* 2013; 36:2720–5. [PubMed: 23757428]
41. Ng M, Freeman MK, Fleming TD, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980–2012. *JAMA.* 2014; 311:183–92. [PubMed: 24399557]
42. IDF Diabetes Atlas: Sixth Edition. International Diabetes Federation; 2014. <http://www.idf.org/diabetesatlas/update-2014> [accessed February 7, 2015]
43. Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustün A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet.* 2011; 377:139–46. [PubMed: 21112082]
44. Chiolero A, Faeh D, Paccaud F, Cornuz J. Consequences of smoking for body weight, body fat distribution, and insulin resistance. *Am J Clin Nutr.* 2008; 87:801–9. [PubMed: 18400700]
45. Aubin HJ, Farley A, Lycett D, Lahmek P, Aveyard P. Weight gain in smokers after quitting cigarettes: meta-analysis. *BMJ.* 2012; 345:e4439. [PubMed: 22782848]
46. Attvall S, Fowelin J, Lager I, Von Schenck H, Smith U. Smoking induces insulin resistance—a potential link with the insulin resistance syndrome. *J Intern Med.* 1993; 233:327–32. [PubMed: 8463765]
47. Eliasson B, Attvall S, Taskinen MR, Smith U. Smoking cessation improves insulin sensitivity in healthy middle-aged men. *Eur J Clin Invest.* 1997; 27:450–6. [PubMed: 9179554]
48. Bergman BC, Perreault L, Hunerdosse D, et al. Novel and reversible mechanisms of smoking-induced insulin resistance in humans. *Diabetes.* 2012; 61:3156–66. [PubMed: 22966072]
49. Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. *Prev Med.* 2003; 37:283–90. [PubMed: 14507483]
50. Balkau B, Vierron E, Vernay M, et al. The impact of 3-year changes in lifestyle habits on metabolic syndrome parameters: the D.E.S.I. R Study. *Eur J Cardiovasc Prev Rehabil.* 2006; 13:334–40. [PubMed: 16926661]
51. Stadler M, Tomann L, Storka A, et al. Effects of smoking cessation on beta-cell function, insulin sensitivity, body weight, and appetite. *Eur J Endocrinol.* 2014; 170:219–27. [PubMed: 24179100]
52. Lycett D, Nichols L, Ryan R, et al. The association between smoking cessation and glycaemic controls in patients with type 2 diabetes: a THIN database cohort study. *Lancet Diabetes Endocrinol.* 2015; 3:423–30. [PubMed: 25935880]

53. Clair C, Rigotti NA, Porneala B, et al. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. *JAMA*. 2013; 309:1014–21. [PubMed: 23483176]
54. Luo J, Rossouw J, Margolis KL. Smoking cessation, weight change, and coronary heart disease among postmenopausal women with and without diabetes. *JAMA*. 2013; 310:94–6. [PubMed: 23821094]
55. Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet*. 2013; 381:133–41. [PubMed: 23107252]
56. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med*. 2013; 368:341–50. [PubMed: 23343063]
57. World Health Organization. WHO report on the global tobacco epidemic, 2013. Geneva, Switzerland: World Health Organization; 2013. http://www.who.int/tobacco/global_report/2013/en/ [accessed February 7, 2015]
58. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380:2224–60. [PubMed: 23245609]
59. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011; 343:d4002. [PubMed: 21784880]
60. Strine TW, Okoro CA, Chapman DP, et al. Health-related quality of life and health risk behaviors among smokers. *Am J Prev Med*. 2005; 28:182–7. [PubMed: 15710274]
61. Chiolerio A, Wietlisbach V, Ruffieux C, Paccaud F, Cornuz J. Clustering of risk behaviors with cigarette consumption: a population-based survey. *Prev Med*. 2006; 42:348–53. [PubMed: 16504277]
62. US Department of Health and Human Services. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2010.
63. US Department of Health and Human Services. The Health Consequences of Involuntary Exposure to Tobacco Smoke. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.
64. World Health Organization. WHO Framework Convention on Tobacco Control. Geneva, Switzerland: World Health Organization; 2009. http://www.who.int/fctc/text_download/en/index.html [accessed June 14, 2015]

Figure 1. Flowchart of the Meta-analysis

*Three studies reported results for both active smoking and passive smoking, all papers reported results for smoking cessation also reported results for active smoking.

Figure 2. Relation of Smoking Intensity with Risk of Incident Type 2 Diabetes

A total of 25 studies reported results for current smoking intensity (cigarettes per day), and 11 studies reported results for cumulative smoking exposure (pack-years); among them, 6 studies reported results for both current smoking intensity and cumulative smoking exposures. In most studies, light smokers referred to those smoked <10 cigarettes per day (or 1-19 pack-years), moderate smokers referred to 10-19 cigarettes per day (or 20-39 pack-years), and heavy smokers were those smoked ≥20 cigarettes per day (or ≥40 pack-years).

Figure 3. Relation of Smoking Cessation with Risk of Incident Type 2 Diabetes

A total of 47 studies reported results comparing former smoking with never smoking, and 10 studies reported results of former smokers by years since smoking cessation.

Table 1
Stratified Analyses of Smoking Status and Risk of Incident Type 2 Diabetes

	Current smoking				Former smoking			
	RR (95% CI) ^a	n of participants (comparisons) ^b	I ² (%)	p for Heterogeneity	RR (95% CI) ^a	n of participants (comparisons) ^c	I ² (%)	p for Heterogeneity
Overall results	1.37 (1.33-1.42)	5853952 (96)	68.6	<0.0001	1.14 (1.10-1.18)	2930391 (56)	59.7	<0.0001
Comparison groups								
Current vs. never	1.40 (1.33-1.47)	2931918 (58)	72.0	<0.0001	-	-	-	-
Current vs. non-current	1.35 (1.27-1.42)	2713305 (34)	56.2	<0.0001	-	-	-	-
Ever vs. never	1.35 (1.16-1.57)	208729 (4)	83.6	<0.0001	-	-	-	-
Smoking intensity								
Light	1.21 (1.10-1.33)	2366372 (23)	84.7	<0.0001	-	-	-	-
Moderate	1.34 (1.27-1.41)	2700146 (34)	69.8	<0.0001	-	-	-	-
Heavy	1.57 (1.47-1.66)	2698826 (32)	69.9	<0.0001	-	-	-	-
Sex ^d								
Men	1.42 (1.34-1.50)	2812898 (39)	71.7	<0.0001	1.16 (1.10-1.22)	1408580 (28)	60.5	<0.0001
Women	1.33 (1.26-1.41)	2737086 (21)	68.7	<0.0001	1.12 (1.05-1.20)	1348057 (14)	75.2	<0.0001
Mixed	1.37 (1.27-1.48)	303968 (40)	62.9	<0.0001	1.11 (1.05-1.18)	173754 (16)	0	0.48
Study Location								
US	1.34 (1.27-1.42)	1384095 (23)	63.8	<0.0001	1.14 (1.08-1.21)	1118575 (16)	73.2	<0.0001
Europe or Oceania	1.39 (1.31-1.47)	2855868 (41)	71.9	<0.0001	1.13 (1.05-1.22)	226951 (17)	36.7	0.065
Asia	1.41 (1.31-1.50)	1613989 (32)	68.4	<0.0001	1.16 (1.09-1.24)	1584865 (23)	52.5	0.002
Ethnicity ^e								
Caucasian Whites	1.42 (1.32-1.53)	505578 (45)	71.0	<0.0001	1.14 (1.08-1.21)	419578 (24)	45.1	0.009
East Asians	1.37 (1.29-1.46)	1645587 (32)	68.0	<0.0001	1.15 (1.09-1.21)	1617963 (25)	48.2	0.004
Others, mixed	1.30 (1.26-1.34)	3699967 (23)	37.6	0.04	1.13 (1.06-1.21)	890030 (11)	69.9	<0.0001
Smoking exposure								
As the main exposure	1.45 (1.37-1.54)	2730778 (41)	72.4	<0.0001	1.15 (1.11-1.20)	2720527 (36)	65.9	<0.0001
As a co-risk factor	1.32 (1.26-1.39)	2991924 (33)	69.5	<0.0001	1.08 (1.03-1.13)	173269 (11)	2.0	0.42
As a confounder	1.31 (1.21-1.42)	131250 (22)	41.0	0.024	1.32 (1.12-1.56)	36595 (9)	47.6	0.054
Measurement of diabetes								

	Current smoking				Former smoking			
	RR (95% CI) *	n of participants (comparisons) ^b	I ² (%)	p for Heterogeneity	RR (95% CI) *	n of participants (comparisons) ^c	I ² (%)	p for Heterogeneity
Biologically screening	1.44 (1.36-1.53)	540281 (55)	62.3	<0.0001	1.17 (1.10-1.25)	408866 (31)	39.4	0.014
Self-report or registry database	1.32 (1.27-1.37)	5313671 (41)	71.8	<0.0001	1.13 (1.08-1.18)	2521525 (25)	70.1	<0.0001
Baseline mean age								
<50 years	1.39 (1.33-1.46)	4871190 (53)	64.8	<0.0001	1.13 (1.08-1.17)	2243623 (30)	35.9	0.028
50 years	1.37 (1.29-1.44)	982762 (43)	72.9	<0.0001	1.17 (1.10-1.23)	686768 (26)	71.7	<0.0001
Baseline mean BMI								
<25	1.39 (1.31-1.46)	2678532 (43)	69.7	<0.0001	1.13 (1.08-1.18)	2430023 (28)	47.6	0.003
25	1.38 (1.31-1.45)	3140211 (46)	69.6	<0.0001	1.17 (1.10-1.24)	485867 (25)	70.3	<0.0001
Not sure	1.29 (1.10-1.52)	35209 (7)	58.2	0.026	1.12 (0.95-1.31)	14501 (3)	0	0.67
Study quality								
Low (score <7)	1.35 (1.29-1.43)	3734072 (48)	66.6	<0.0001	1.15 (1.08-1.23)	1077649 (24)	59.5	<0.0001
High (score ≥7)	1.39 (1.33-1.46)	2119880 (48)	69.5	<0.0001	1.15 (1.10-1.19)	1852742 (32)	48.0	0.002
Follow-up years								
<10 years	1.38 (1.31-1.45)	3878524 (51)	69.8	<0.0001	1.15 (1.09-1.22)	1236298 (31)	59.0	<0.0001
10 years	1.38 (1.31-1.44)	1975428 (45)	67.1	<0.0001	1.15 (1.10-1.19)	1694093 (25)	49.9	0.003
Publication year								
On and before 2000	1.52 (1.28-1.81)	89724 (12)	54.2	0.013	1.24 (1.07-1.44)	72613 (6)	25.1	0.25
2001-2009	1.40 (1.33-1.46)	3689353 (45)	62.7	<0.0001	1.13 (1.08-1.19)	1031048 (25)	27.1	0.11
On and after 2010	1.33 (1.26-1.40)	2074875 (40)	75.0	<0.0001	1.14 (1.08-1.19)	1826730 (25)	74.0	<0.0001
Adjustment variables								
BMI or waist circumference								
Yes	1.39 (1.34-1.44)	5687250 (80)	66.2	<0.0001	1.15 (1.11-1.19)	2804071 (51)	62.3	<0.0001
No	1.30 (1.13-1.50)	166702 (16)	75.1	<0.0001	1.08 (0.99-1.19)	126320 (5)	0	0.44
Physical activity								
Yes	1.37 (1.31-1.44)	2996391 (52)	73.2	<0.0001	1.13 (1.09-1.17)	2755812 (41)	61.6	<0.0001
No	1.39 (1.31-1.46)	2857561 (44)	61.5	<0.0001	1.28 (1.14-1.45)	174579 (15)	49.6	0.015
Dietary variables								
Yes	1.35 (1.27-1.44)	1174005 (18)	71.3	<0.0001	1.13 (1.09-1.18)	958366 (12)	46.0	0.040
No	1.39 (1.33-1.44)	679947 (78)	68.3	<0.0001	1.16 (1.10-1.22)	72025 (44)	61.9	<0.0001

	Current smoking				Former smoking			
	RR (95% CI) ^a	n of participants (comparisons) ^b	I ² (%)	p for Heterogeneity	RR (95% CI) ^a	n of participants (comparisons) ^c	I ² (%)	p for Heterogeneity
Alcohol intake								
Yes	1.41 (1.35-1.48)	2864361 (52)	70.2	<0.0001	1.14 (1.10-1.19)	2616816 (36)	67.7	<0.0001
No	1.33 (1.26-1.40)	2989591 (44)	65.2	<0.0001	1.15 (1.06-1.25)	313575 (20)	30.5	0.10
Blood pressures								
Yes	1.36 (1.30-1.42)	3298059 (50)	65.9	<0.0001	1.12 (1.07-1.18)	654787 (32)	58.8	<0.0001
No	1.40 (1.32-1.48)	2555893 (46)	71.0	<0.0001	1.16 (1.11-1.22)	2275604 (24)	54.0	0.001
Blood lipids								
Yes	1.43 (1.33-1.52)	468754 (38)	66.2	<0.0001	1.18 (1.09-1.29)	369433 (25)	66.2	<0.0001
No	1.35 (1.29-1.40)	5385198 (58)	69.5	<0.0001	1.13 (1.10-1.17)	256098 (31)	41.8	0.009
Glycemic parameters								
Yes	1.48 (1.35-1.62)	303359 (32)	71.1	<0.0001	1.20 (1.07-1.35)	196413 (16)	54.4	0.005
No	1.35 (1.30-1.39)	5550593 (64)	66.7	<0.0001	1.13 (1.09-1.17)	2733978 (40)	61.5	<0.0001

Abbreviations: RR, relative risk; NA, not available.

^a The results are presented using the random-effects model.

^b A total of 12 studies reported their results separately for men and women, and thus there were 96 comparisons from 84 studies.

^c A total of 9 studies reported their results separately for men and women, and thus there were 56 comparisons from 47 studies.

^d Four studies³¹⁻³⁴ further reported their results by sex, and thus there were 100 comparisons from 84 studies.

^e One study³⁵ further reported their results by ethnicity (Caucasian, Japanese American, and Native Hawaiian), and thus there were 100 comparisons from 84 studies.