Smoking cessation and weight change in relation to cardiovascular disease incidence and mortality in people with type 2 diabetes: a population-based cohort study

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Summary

Background To reduce their overall substantially increased risk of cardiovascular disease and premature mortality, smoking cessation is especially important for people with diabetes. However, the effect of weight change after quitting smoking on the long-term health consequences of smoking cessation is unclear. We aimed to examine smoking cessation and subsequent weight change in relation to incident cardiovascular disease events and mortality among adults with type 2 diabetes.

Methods In this population-based cohort study, we analysed data from people with type 2 diabetes from two prospective cohorts in the USA: the Nurses' Health Study (1976–2014) and the Health Professionals Follow-Up Study (1986–2014). We included participants from both cohorts who either had prevalent type 2 diabetes or were diagnosed during the study, and who were either current smokers or never smokers without cardiovascular disease or cancer at diagnosis of diabetes. Information on demographics, newly diagnosed diseases, medical history, and lifestyle factors, including smoking status and weight change, was updated every 2 years through validated questionnaires. We assessed the incidence of cardiovascular disease and all-cause and cause-specific mortality among recent quitters (within 6 years of stopping) and long-term quitters (>6 years) associated with weight change within 6 years of smoking cessation among people with type 2 diabetes. We did a multivariable-adjusted Cox proportional hazard models to estimate hazard ratios (HRs) for the associations of smoking cessation and weight change on the outcomes.

Findings Of 173 229 total cohort participants (121 700 from the Nurses' Health Study and 51 529 from the Health Professionals Follow-Up Study), 10 809 people with type 2 diabetes were included in the incident cardiovascular disease analysis and 9688 were included in the mortality analysis. 2580 incident cases of cardiovascular disease occurred during 153 166 person-years of follow-up, and 3827 deaths occurred during 152 811 person-years of follow-up. Recent quitters (2–6 consecutive years since smoking cessation) without weight gain within the first 6 years of quitting had a significantly lower risk of cardiovascular disease than people who continued to smoke (multivariable-adjusted HR 0·83 [95% CI 0·70–0·99] among all recent quitters, 0·77 [0·62–0·95] among recent quitters without weight gain, 0·99 [0·70–1·41] among recent quitters with weight gain of 0·1–5·0 kg, 0·89 [0·65–1·23] among recent quitters with weight gain of >5·0 kg, and 0·72 [0·61–0·84] among longer-term quitters [>6 consecutive years since smoking cessation]). Weight gain within 6 years after smoking cessation did not attenuate the inverse relation between long-term cessation and all-cause mortality (multivariable-adjusted HR 0·69 [95% CI 0·58–0·82] among long-term quitters without weight gain, 0·57 [0·45–0·71] among long-term quitters with weight gain of 0·1–5·0 kg, and 0·51 [0·42–0·62] among long-term quitters with weight gain of >5·0 kg), with similar results observed for cardiovascular disease and cancer mortality.

Interpretation Smoking cessation without subsequent weight gain is associated with a reduced risk of cardiovascular disease and mortality among smokers with type 2 diabetes. Weight gain after smoking cessation attenuates the reduction in risk of developing cardiovascular disease, but does not attenuate the beneficial effect of smoking cessation with respect to mortality. These findings confirm the overall health benefits of quitting smoking among people with type 2 diabetes, but also emphasise the importance of weight management after smoking cessation to maximise its health benefits.

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Introduction

Lifestyle modification has a fundamental role in the prevention and management of type 2 diabetes.[1] For people with diabetes, the risk of developing cardiovascular disease and other morbidities is significantly increased by both smoking and hyperglycaemia.[1,2] Therefore, smoking cessation is strongly advised.[1,3] However, smoking cessation is often accompanied by weight gain,[4] which is a potential health concern for people with diabetes because it might result in poor diabetes control and increased risk

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Research in context

Evidence before this study

We searched PubMed, Web of Science, and Google Scholar for articles published from database inception up to March 31, 2019, with no language restrictions, eith search terms including "smoking cessation", "quitting smoking", "weight change", "weight gain", "cardiovascular disease", "myocardial infarction", "coronary heart disease", "stroke", and "mortality". We identified two studies that examined the associations of smoking cessation and weight change after quitting smoking with cardiovascular disease among patients with diabetes. The findings from one study suggested that smoking cessation was non-significantly associated with a reduced risk of cardiovascular disease among patients with diabetes, independent of weight change, whereas the findings the other study suggested that the association with reduced risk of coronary heart disease was attenuated by weight gain after smoking cessation. These studies shared some limitations, such as small sample size and use of point prevalence abstinence, which could not reflect dynamic changes in smoking status during follow-up.

Added value of this study

With a relatively large sample size and repeated assessments of smoking status and bodyweight after diagnosis of type 2 diabetes, our study showed that smoking cessation without subsequent weight gain was associated with significantly reduced risk of cardiovascular disease and mortality. Weight gain after smoking cessation attenuated the beneficial association between cessation and incidence of cardiovascular disease, but not the beneficial effect on all-cause and cause-specific mortality.

Implications of all the available evidence

Our findings confirm the long-term benefits of smoking cessation with respect to reducing mortality among people with type 2 diabetes, irrespective of weight change after cessation. However, since weight gain after cessation attenuated the beneficial effects of smoking cessation on the risk of incident cardiovascular disease, these findings also emphasise the importance of bodyweight control after smoking cessation in maximising the cardiovascular health benefits of quitting smoking among people with type 2 diabetes.

of developing complications.[5,6] Whether weight gain after smoking cessation attenuates the long-term reductions in risk of major complications due to diabetes that are associated with quitting smoking is uncertain, with previous studies having inconsistent findings.[7,8] Furthermore, these existing studies were limited by small sample sizes[7,8] and the use of point prevalence measures of smoking abstinence, which might not reflect dynamic changes in smoking status during follow-up.[8]

To address the limitations of previous studies and to further clarify the role of weight gain in the association between smoking cessation and risk of cardiovascular disease and mortality in people with type 2 diabetes, we investigated smoking cessation and weight change in association with subsequent risk of total cardiovascular disease, coronary heart disease, stroke, and all-cause and cause-specific mortality among adults with type 2 diabetes who participated in the Nurses' Health Study or the Health Professionals Follow-Up Study.[9,10]

Methods

Study design and population

In this prospective, population-based cohort study, we used data from two cohorts of medical professionals in the USA. The Nurses' Health Study, established in 1976, is an ongoing prospective cohort study of 121700 female nurses aged 30–55 years from 11 US states.[9] The Health Professionals Follow-Up Study, initiated in 1986, is an ongoing prospective cohort study of 51529 male health professionals aged 40–75 years from 50 US states.[10] Detailed information on lifestyle factors and medical conditions was updated every 2 years through validated questionnaires. The cumulative follow-up rate exceeded 90% in both cohorts. More details have been described previously.[11,12]

For the current study, we included participants from both cohorts with a diagnosis of type 2 diabetes at the time of enrolment into the cohort (1976 for the Nurses' Health Study and 1986 for the Health Professionals Follow-Up Study), and those diagnosed with type 2 diabetes during follow-up (up to 2014). We only included people with type 2 diabetes who were either current smokers or never smokers at time of diabetes diagnosis, excluding those who were past smokers at diagnosis. We also excluded participants who had cancer, cardiovascular disease, or chronic obstructive pulmonary disease (COPD) before they were diagnosed with type 2 diabetes. The exclusion of these individuals helped to reduce the probability that participants quit smoking due to existing diseases. For all analyses, we also excluded participants with missing smoking status information in two or more consecutive 2-year follow-up survey cycles.

This study was approved by the institutional review boards at the Harvard TH Chan School of Public Health and Brigham and Women's Hospital (both in Boston, MA, USA), and the return of completed questionnaires was considered to be implied consent.

Assessments of demographic and clinical characteristics

In each 2-year survey cycle, we identified and defined participants who quit smoking as those who reported being a smoker in the previous cycle but as a past smoker in the current cycle, assuming the beginning of the

previous cycle as the onset of cessation. Duration of smoking cessation was counted from the onset of quitting to a relapse in smoking, occurrence of study outcomes, or the end of follow-up (appendix p 2). Previous studies have shown that weight gain associated with smoking cessation mainly occurs during roughly the first 6 years after quitting smoking.[13,14] As such, the status of those who had quit smoking was defined by use of the following mutually exclusive terms: transient quitters (past smokers who reported as current smokers in the immediately preceding cycle and the immediately following cycle), recent quitters (had previously reported as a current smoker and then reported as a past smoker for 2–6 consecutive years), and long-term quitters (had previously reported as a current smoker and then reported as a past smoker for >6 consecutive years). All analyses were based on person-time in these time windows since smoking cessation. We replaced missing smoking information with valid assessments in the previous cycle to ensure that changes in smoking status were recent. In these cohorts, self-reported smoking status and bodyweight have been shown to be highly accurate.[15,16]

We focused on weight change within 6 years after quitting, which has been found to be the period most relevant to weight change after smoking cessation.[13,14] Missing bodyweight estimates were replaced with last available values. Weight changes were grouped into no weight gain, an increase of 0·1–5·0 kg, and an increase of more than 5·0 kg.[14]

Participants who reported a physician's diagnosis of type 2 diabetes in any of the 2-yearly questionnaires were sent a validated supplementary questionnaire regarding symptoms, diagnostic tests, and glucose-lowering treatment. Before the release of the American Diabetes Association criteria in 1997, the National Diabetes Data Group criteria were used to define diagnosis of type 2 diabetes.[17] An HbA_{1c} of 6·5% (48 mmol/mol) or higher was further included in the diagnosis criteria after 2010. More details have been reported elsewhere.[17]

Incident cardiovascular disease was defined as fatal or non-fatal coronary heart disease (including non-fatal myocardial infarction and coronary artery bypass graft surgery) or percutaneous coronary intervention and fatal or non-fatal stroke. Permission was requested as part of the studies to review medical records when participants reported non-fatal cardiovascular disease events on any questionnaires. All medical records were reviewed by physicians, who were masked to the participant questionnaire data, to confirm or refute non-fatal cardiovascular disease events. Deaths were identified by reports from next of kin, US postal authorities, or searching of the National Death Index. Fatal cardiovascular disease events were identified and confirmed or refuted via review of hospital records, death certificates, or autopsy reports. Cardiovascular disease mortality was defined by International Classification of Diseases ninth revision (ICD-9) codes 390–459 and cancer mortality was defined by ICD-9 codes 140–208. More details have been described previously.[18]

In the 2-yearly follow-up questionnaires, information was updated on demographics, physical activity, alcohol consumption, menopausal status and use of post-menopausal hormone therapy (women only), medical history (including use of aspirin and lipid-lowering drugs), family history of myocardial infarction or cancer, and presence of hypertension, hypercholesterolaemia, cardiovascular disease, cancer, or other diseases. We calculated BMI as self-reported weight in kg divided by the square of self-reported height in metres (kg/m²). Physical activity was estimated as metabolic equivalents per week based on the average time spent on various activities in h, weighted by the intensity level.[17] Dietary intake was assessed with a validated semi-quantitative food frequency questionnaire, with 131 food items, administered every 2–4 years.[17] Overall diet quality was assessed with the Alternative Health Eating Index score (ranging 10–110, with higher scores indicating a healthier diet).[18]

See Online for appendix

Statistical analysis

Our primary analyses assessed incidence of cardiovascular disease and mortality. For analysis of incidence of cardiovascular disease, we focused on risk of cardiovascular disease during both the recent quitting window (a consecutive 2–6 years since smoking cessation) and long-term quitting window (>6 consecutive years since cessation). For mortality analyses, to minimise potential serious reverse-causation bias (ie, deaths due to some severe diseases that result in both smoking cessation and weight loss), we focused on mortality in the long-term quitting window and excluded participants who died within 6 years of quitting smoking. As such, we explicitly addressed the question of whether weight change following smoking cessation affects long-term survival among people with type 2 diabetes who have survived the first 6 years of quitting. In a secondary analysis, we also examined mortality during the first 2–6 years after quitting among recent quitters, by weight change during the same period.

We calculated person-time from the date of diabetes diagnosis to occurrence of study outcomes, final return of a valid follow-up questionnaire, or the end of follow-up (June 30, 2014, for the Nurses' Health Study and Jan 30, 2014, for the Health Professionals Follow-Up Study), whichever came first. For cardiovascular disease analyses, follow-up was further censored at a diagnosis of cancer because this disease is likely to lead to changes in both smoking status and bodyweight. For mortality analyses, we stopped updating smoking status after diagnosis of cardiovascular disease, cancer, or COPD to minimise the reverse-causation bias caused by the so-called sick quitter effect.

We used Cox proportional-hazard models to estimate hazard ratios (HRs) and 95% CIs for the associations of smoking cessation and weight change with total

incidence of cardiovascular disease, coronary heart disease, and stroke, and all-cause and cause-specific mortality. In multivariable models, we adjusted for age (years), diabetes duration (years), sex (male or female), white ethnic origin (yes or no), BMI assessed in the cycle before diabetes was diagnosed (<25·0, 25·0–29·9, 30·0–35·0, >35·0 kg/m²), physical activity (metabolic equivalent h per week in quintiles), alcohol consumption (0, 0·1–4·9, 5·0–14·9, ≥15·0 g per day), total energy intake (kcal/day in quintiles), Alternative Health Eating Index score (in quintiles), family history of myocardial infarction before age 60 years (yes or no), family history of cancer (yes or no; for mortality analysis only), current aspirin use (yes or no), current multivitamin use (yes or no), presence of hypertension (yes or no), presence of hypercholesterolaemia (yes or no), and use of diabetes medication (insulin, oral medication, or others). We used time-varying covariates in the multivariable models, apart from sex, ethnic origin, BMI shortly before diabetes diagnosis, and family history of myocardial infarction and cancer, for which baseline assessment was adjusted. We tested the proportional-hazards assumption using a likelihood ratio test comparing models with and without multiplicative interaction terms between exposure and calendar year, and we did not find evidence of violation of the proportional hazards assumption. To examine the association between duration of smoking cessation and study outcomes we fitted a cubic spline regression model with three knots. We did tests for non-linearity based on the likelihood ratio test comparing two models: one with only the linear term and the other with the linear and the cubic spline terms.

We did several sensitivity analyses to test the robustness of our findings. We repeated the primary analyses comparing those with no weight gain (≤0 kg) versus those with weight gain (>0 kg). Additionally, we repeated the primary analyses with recent quitters defined as having quit for 2–4 consecutive years and 2–8 consecutive years; grouping participants by tertiles of weight change; with the start of quitting defined as the beginning of the cycle that participants first reported being past smokers. Additionally, although most women in our study were postmenopausal, we further included menopausal status and use of postmenopausal hormone therapy (premenopausal, never users of postmenopausal hormone therapy, past users of postmenopausal hormone therapy, or current users of postmenopausal hormone therapy) in the model as variables. We further adjusted for other medication use, including antihypertensive drugs and lipid-lowering drugs. Finally, we excluded participants who lost more than 30 kg of bodyweight after smoking cessation within 6 years to minimise potential reverse-causation bias.

We did all statistical analyses using SAS (version 9.4). We considered a two-sided p value of less than 0·05 to be significant.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 173 229 total cohort participants (121 700 from the Nurses' Health Survey and 51 529 from the Health Professionals Follow-Up Study), 10 809 people with type 2 diabetes were included in the incident cardiovascular disease analysis and 9688 were included in the mortality analysis (appendix p 1). Characteristics of person-years according to smoking status for participants included in the incident cardiovascular disease analysis are shown in table 1. Quitters were usually older, had a higher prevalence of hypertension, a higher physical activity level, and a better diet quality than did current smokers. Among recent quitters, those who gained weight tended to be older and had a higher prevalence of hypercholesterolaemia, a lower prevalence of family history of myocardial infarction, and a lower diet quality than those who did not gain weight within 6 years after quitting (table 1). Characteristics of person-years according to smoking status for participants included in the mortality analysis are in the appendix (p 3).

In the cardiovascular disease analysis, we documented 2580 incident cases (including 607 stroke cases) during 153 166 person-years of follow-up. Among all 10 809 participants included in the cardiovascular disease incidence analysis, 2633 (24·4%) were current smokers at diagnosis of type 2 diabetes. The median weight gain among quitters after smoking cessation within 6 years was 3·2 kg (IQR –0·9 to 6·8). Recent quitters without weight gain within the 2–6 years since smoking cessation had a significantly lower risk of cardiovascular disease than did those who continued to smoke (table 2). The HRs for cardiovascular disease after multivariable adjustment for diabetes duration, BMI assessed shortly before diabetes diagnosis, other lifestyle and dietary factors, and medication use by smoking status are shown in table 2. Compared with those who continued to smoke, recent quitters (2–6 consecutive years since smoking cessation) without weight gain within the first 6 years of quitting had a significantly lower risk of cardiovascular disease and coronary heart disease. In a sensitivity analysis, when grouping participants into those with no weight gain versus those with any weight gain and the results were similar: compared with those who continued to smoke, the multivariable-adjusted HRs for cardiovascular disease were 0·77 (95% CI 0·62 to 0·95) among recent quitters without weight gain, and 0·94 (0·73 to 1·20) among recent quitters with weight gain (table 2). We identified an inverse association between long-term quitting and risk of cardiovascular disease according to

	Current smokers	Recent quitters, by weight gain within 2–6 years after quitting			Long-term quitters	Transient quitters	Never smokers
		≤0 kg	0·1–5·0 kg	>5·0 kg			
Person-years*	20 983	8471	1818	2154	16 742	600	102 398
Age, years	59·2 (9·9)	59·9 (11·2)	61·2 (9·6)	61·6 (9·0)	66·7 (9·6)	59·5 (9·5)	66·0 (10·6)
BMI shortly before diabetes diagnosis, kg/m²	28·7 (6·0)	29·8 (6·6)	27·8 (5·8)	29·4 (6·3)	29·6 (5·9)	29·4 (5·6)	30·7 (6·0)
Ethnic origin, %							
White	95·7%	94·8%	94·7%	95·1%	94·1%	91·4%	92·4%
Black	1·3%	1·6%	1·8%	1·8%	2·0%	3·0%	2·5%
Asian	1·6%	1·8%	2·0%	2·1%	1·9%	2·8%	2·7%
Other	1·4%	1·8%	1·5%	1·0%	2·0%	2·7%	2·4%
Self-reported hypertension	63·4%	64·6%	64·4%	68·4%	67·7%	72·6%	70·1%
Self-reported high cholesterol	58·1%	50·6%	57·3%	67·3%	60·9%	58·0%	60·0%
Family history of myocardial infarction	29·9%	28·5%	28·0%	26·6%	29·8%	27·3%	26·5%
Multivitamin use	36·4%	35·0%	40·9%	38·1%	43·7%	36·4%	41·4%
Physical activity, MET h per week	5·0 (1·0–15·2)	7·5 (2·3–20·6)	8·4 (2·5–20·2)	5·9 (1·5–15·4)	7·7 (2·0–20·2)	4·2 (0·9–15·4)	7·4 (2·1–18·7)
Alternative Healthy Eating Index	51·3 (11·4)	53·8 (12·2)	52·8 (11·0)	52·0 (10·9)	55·3 (11·8)	52·4 (10·5)	53·9 (11·8)
Alcohol consumption, g/day	0·0 (0·0–4·7)	0·0 (0·0–5·3)	0·0 (0·0–5·5)	0·0 (0·0–2·7)	0·0 (0·0–3·8)	0·0 (0·0–3·2)	0·0 (0·0–1·2)
Total energy intake, kcal/day	1624·1 (581·5)	1672·7 (566·9)	1675·0 (535·0)	1669·1 (561·8)	1704·5 (560·8)	1573·1 (579·8)	1694·9 (568·1)

Data are person-years in mean (SD), median (IQR), or percentage. MET=metabolic equivalent tasks. *Person-years are based on the analyses for incident cardiovascular disease.

Table 1: **Characteristics of person-years according to smoking status among participants with type 2 diabetes**

weight change within 6 years after quitting (appendix p 4), although some of the associations were not significant, probably because of low statistical power. We identified a linear inverse relation between duration of smoking cessation and incidence of cardiovascular disease ($p_{linearity}$=0·011; figure 1). Similar patterns of associations between duration of smoking cessation and coronary heart disease and stroke were apparent (table 2), although some of the associations were not significant, probably because of low statistical power.

In our mortality analysis, we documented 3827 deaths during 152 811 person-years of follow-up. Notably, in this analysis, we focused on long-term quitters and their mortality after they survived the first 6 consecutive years after cessation. Weight gain within 6 years after smoking cessation did not attenuate the inverse association between long-term quitting and mortality (table 3). Compared with participants who continued to smoke, the multivariable-adjusted HRs for all-cause mortality were 0·69 (95% CI 0·58–0·82) among long-term quitters without weight gain within 6 years after quitting, 0·57 (0·45–0·71) among long-term quitters with weight gain of 0·1–5·0 kg, and 0·51 (0·42–0·62) among long-term quitters with weight gain of more than 5·0 kg. In a sensitivity analysis, when grouping into no weight gain versus wight gain within 6 years of quitting, similar results were observed: compared with those who continued to smoke, the multivariable-adjusted HRs for all-cause mortality were 0·69 (95% CI 0·58–0·82) among long-term quitters without weight gain and 0·54 (0·45–0·63) among long-term quitters with weight gain. We identified an inverse linear relationship between duration of smoking cessation and all-cause mortality ($p_{linearity}$<0·0001; figure 2).

In a secondary analysis among recent quitters, we modelled the association between smoking cessation and mortality within the first 2–6 years since quitting (without excluding those who died within 6 years after quitting; appendix p 5). Compared with participants who continued to smoke, the multivariable-adjusted HRs for all-cause mortality were 0·84 (95% CI 0·71–0·99) among recent quitters without weight gain within 6 years after quitting, 0·73 (0·43–1·24) among recent quitters with weight gain of 0·1–5·0 kg, and 0·46 (0·26–0·83) among recent quitters with weight gain of more than 5·0 kg. Similar patterns of associations were apparent for cardiovascular disease and cancer mortality (table 3; appendix p 5).

In sensitivity analysis, similar results to the primary analyses were seen when recent quitters were defined as quitting for 2–4 consecutive or 2–8 consecutive years rather than 2–6 consecutive years (appendix pp 6–7), when tertiles of weight change after cessation were used (appendix pp 8–9), and when the start of cessation was defined as the beginning of the cycle that participants first reported being past smokers (appendix pp 10–11). Furthermore, similar results were seen when menopausal status and use of postmenopausal hormone therapy were further adjusted for, when use of antihypertensive drugs and lipid-lowering drugs were further adjusted for, and when participants who lost more than 30 kg of bodyweight after smoking cessation within 6 years were excluded (data not shown).

	Current smokers	Recent quitters	Recent quitters, by weight gain within 2–6 years after quitting			Long-term quitters	Transient quitters	Never smokers
			≤0 kg	0·1–5·0 kg	>5·0 kg			
Cardiovascular disease								
Person-years	20 983	12 443	8471	1818	2154	16 742	600	102 398
Number of events	454	231	143	40	48	389	9	1497
Crude incident rate per 1000 person-years	21·64	18·56	16·88	22·00	22·28	23·23	15·00	14·62
Multivariable-adjusted hazard ratio (95% CI)	1·00 (ref)	0·83 (0·70–0·99)	0·77 (0·62–0·95)	0·99 (0·70–1·41)	0·89 (0·65–1·23)	0·72 (0·61–0·84)	0·63 (0·30–1·32)	0·59 (0·53–0·67)
Coronary heart disease								
Number of events	355	185	119	33	33	319	8	1134
Crude incident rate per 1000 person-years	16·92	14·87	14·05	18·15	15·32	19·05	13·33	11·07
Multivariable-adjusted hazard ratio (95% CI)	1·00 (ref)	0·82 (0·67–1·00)	0·80 (0·63–1·00)	1·02 (0·69–1·50)	0·75 (0·51–1·11)	0·78 (0·66–0·94)	0·82 (0·38–1·73)	0·58 (0·50–0·66)
Stroke								
Number of events	102	49	26	8	15	70	2	383
Crude incident rate per 1000 person-years	4·86	3·93	3·07	4·40	6·96	4·18	3·33	3·74
Multivariable-adjusted hazard ratio (95% CI)	1·00 (ref)	0·87 (0·60–1·27)	0·70 (0·44–1·12)	1·03 (0·48–2·23)	1·30 (0·72–2·37)	0·51 (0·36–0·73)	0·33 (0·04–2·53)	0·67 (0·52–0·86)

Incident cardiovascular disease was defined as fatal and non-fatal coronary heart disease (including non-fatal myocardial infarction and coronary artery bypass graft surgery) or percutaneous coronary intervention and fatal and non-fatal stroke..

Table 2: **Association between smoking cessation and the incidence of cardiovascular disease, coronary heart disease, and stroke among people with type 2 diabetes, by smoking status**

Figure 1: **Association between duration of smoking cessation and incidence of cardiovascular disease among people with type 2 diabetes**
The shaded area indicates the 95% CIs.

Discussion

Among US men and women with type 2 diabetes from two large prospective cohort studies, smoking cessation without weight gain was associated with a lower risk of incident cardiovascular disease and all-cause and cause-specific mortality. Weight gain after cessation of smoking attenuated the inverse association with the risk of incident cardiovascular disease, but the long-term benefits of smoking cessation on reducing mortality were independent of change in bodyweight. These associations were independent of established risk factors, including duration of diabetes, BMI before diagnosis of diabetes, lifestyle and dietary factors, and medication use.

Smoking is a leading cause of many chronic diseases and premature death, and quitting smoking substantially reduces these risks.[19,20] Smoking cessation is particularly important for people with type 2 diabetes because their risk of developing cardiovascular disease or other morbidities is substantially augmented by both smoking and insulin resistance or glycaemia.[1,2] However, smoking cessation is often accompanied by weight gain (eg, mean weight gain of 4·0–5·0 kg after 1 year of abstinence),[4] which is a risk factor for cardiometabolic diseases and might dilute the health benefits of quitting.[6] Previous studies among apparently healthy individuals showed that excessive weight gain (eg, ≥5 kg) after smoking cessation could lead to a short-term (eg, 5–7 years after quitting) increase in the risk of developing type 2 diabetes,[14,21] deterioration in cardiovascular risk factors,[22] and attenuation of the protective effect on cancer;[23] however, data from other studies suggested that weight gain after quitting smoking did not modify the associations between smoking cessation and risk of myocardial infarction, stroke, and mortality in the general population.[14,24,25] Our previous analysis in largely healthy individuals showed that weight gain was associated with a transient increased risk of developing type 2 diabetes, although the reduction in mortality due to cardiovascular disease and total mortality was independent of weight gain.[14]

	Current smokers	Long-term quitters, by weight gain within 2–6 years after quitting			Never smoker
		≤0 kg	0·1–5·0 kg	>5·0 kg	
All-cause mortality					
Person-years	23 921	5184	2839	3806	117 061
Number of events	721	269	121	156	2560
Crude incident rate per 1000 person-years	30·14	51·89	42·62	40·99	21·87
Multivariable-adjusted hazard ratio (95% CI)	1·00 (ref)	0·69 (0·58–0·82)	0·57 (0·45–0·71)	0·51 (0·42–0·62)	0·40 (0·36–0·44)
Cardiovascular disease mortality					
Number of events	242	98	45	45	874
Crude incident rate per 1000 person-years	10·11	18·90	15·85	11·82	7·47
Multivariable-adjusted hazard ratio (95% CI)	1·00 (ref)	0·84 (0·63–1·12)	0·66 (0·46–0·95)	0·47 (0·32–0·67)	0·45 (0·38–0·53)
Cancer mortality					
Number of events	205	58	24	36	507
Crude incident rate per 1000 person-years	8·57	11·19	8·45	9·46	4·33
Multivariable-adjusted hazard ratio (95% CI)	1·00 (ref)	0·71 (0·50–0·99)	0·53 (0·33–0·84)	0·55 (0·37–0·83)	0·33 (0·27–0·39)

Mortality analyses excludes individuals who died within 6 years of smoking. No deaths were recorded among transient quitters.

Table 3: **Association between smoking cessation and all-cause and cause-specific mortality among individuals with type 2 diabetes**

Evidence regarding the links between smoking cessation, weight change, and cardiometabolic consequences in people with type 2 diabetes is fairly sparse. In comparison with the general population, people with diabetes are at a particularly high risk of developing cardiovascular disease, which is the primary complication of diabetes, and premature death.[26] Some studies have suggested that smoking cessation among people with type 2 diabetes could also result in short-term weight gain, temporary deterioration in glycaemic control, and worsening of some diabetes symptoms.[27] Evidence regarding whether weight gain after smoking cessation would attenuate the benefits of quitting on cardiovascular disease events among people with diabetes is inconsistent.[7,8] Among 445 adults with diabetes from the Framingham Offspring Study, recent quitters (≤4 years) and long-term quitters (>4 years) had a non-significantly lower risk of cardiovascular disease events than did those who continued to smoke, and the results were largely unchanged after further adjustment for post-cessation weight change.[7] By contrast, among 6338 postmenopausal women with diabetes who participated in the Women's Health Initiative cohort, weight gain after smoking cessation mitigated the association between quitting and coronary heart disease, especially for those who gained 5 kg or more, although only eight cases of coronary heart disease were identified among the recent quitters.[8] In the present study, with longitudinal repeated assessments of smoking status and bodyweight during three decades of follow-up in two large, prospective cohort studies, we identified an inverse association between smoking cessation and risk of cardiovascular disease among quitters who did not gain weight, whereas among quitters who gained weight this association was not apparent. This finding is in line with accumulating evidence suggesting that excess weight gain could result in alterations in lipids, blood pressure, coagulation, and inflammation, and subsequently endothelial dysfunction and atherosclerosis.[28]

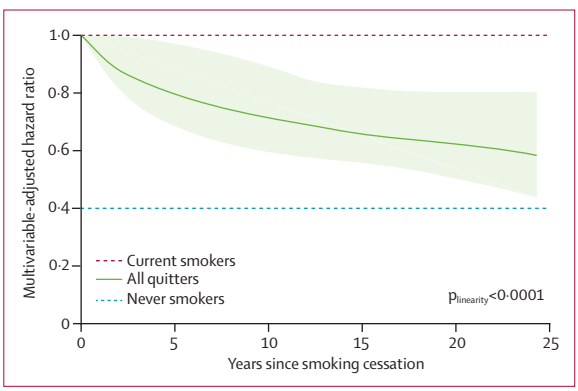

Figure 2: **Association between duration of smoking cessation and all-cause mortality among people with type 2 diabetes**
The shaded area indicates the 95% CI.

To date, no previous study has examined whether weight gain after smoking cessation would affect the reductions in all-cause and cause-specific mortality seen among smokers with type 2 diabetes. Considering the potential reverse-causation bias in mortality analysis (ie, patients with diabetes who died soon after quitting were likely to have a severe disease that resulted in both smoking cessation and weight loss), we analysed

long-term quitters who had survived the first 6 years after smoking cessation. We found that long-term quitters had substantially lower all-cause and cancer mortality and incidence of cardiovascular disease, irrespective of weight gain within the first 6 years after quitting. Interestingly, long-term quitters with weight gain of more than 5 kg seemed to have a lower mortality than those with weight gain of 0·1–5 kg or those without weigh gain, although a cautious interpretation is warranted because this finding might still somewhat reflect reverse causality. Nevertheless, these data suggest that weight gain did not attenuate the reductions in mortality seen after long-term cessation of smoking, and preventing excessive weight gain might maximise the health benefits of smoking cessation on reducing cardiovascular disease complications among people with type 2 diabetes. These findings are of substantial public health significance, since the fear of weight gain after smoking cessation is the main reason for not attempting to quit smoking or for relapsing after a short attempt for many people.[6,29]

The strengths of our study include the prospective design of the cohorts, fairly large study populations including both men and women, repeated assessments of smoking status and bodyweight after diabetes diagnosis, long-term follow-up with a high retention rate, careful adjustments for many potential risk factors, and analysis of several disease outcomes including total cardiovascular disease, all-cause mortality, and cause-specific mortality.

Our study also has several limitations that should be considered. First, our study participants were all health professionals and most were of white ethnic origin. Although the relative homogeneity in socioeconomic status and ethnicity potentially minimises confounding by these factors, it also restricts the generalisability of our findings to other populations. Second, measurement errors in self-reported assessments of smoking status and bodyweight are inevitable, although the high accuracy of the self-reports has been shown in validation studies.[15,16] Third, the exact date of quitting smoking was not available and therefore the assessments of smoking cessation duration and related weight changes were subject to possible misclassification. In these prospective cohorts, such measurement errors were likely to be non-differential and more likely to bias the associations towards the null,[30] although we cannot rule out the possibility that errors in the measurement confounders might also bias the true association away from the null. Fourth, if quitters under-reported weight gain or if they relapsed into smoking but reported continued cessation due to social-desirability bias, the true association might have been attenuated towards the null because these participants still had an increased disease risk. Additionally, we could not capture relapses between two follow-up survey cycles. Fifth, our study did not have direct measurements of glycaemic control and severity of diabetes, although the results did not change significantly when we adjusted for duration of diabetes or use of insulin and glucose-lowering drugs. Additionally, we did not acquire information of nicotine use, vaping, or other smoking cessation interventions, the effects of which on associations with health outcomes requires further investigation. Sixth, our study did not have enough power to test whether sex differences exist in the associations identified, which warrants further investigation. Finally, the role of confounding by genetic susceptibility or psychosocial stress and residual confounding due to measurement errors of covariates or chance could not be entirely excluded.

Our findings from these two large prospective cohort studies suggest that smoking cessation without subsequent weight gain is significantly associated with a reduced risk of total cardiovascular disease, coronary heart disease, and premature death among people with type 2 diabetes. Weight gain after smoking cessation attenuates the inverse association with the incidence of cardiovascular disease, although the reduction of all-cause and cause-specific mortality persists in quitters who gain weight. These data provide evidence that not only supports the overall health benefits of quitting smoking in the prevention of morbidity and mortality among individuals with type 2 diabetes, but also emphasises the importance of weight management after smoking cessation to maximise its health benefits.

Contributors

GL and QS conceived and designed the study. GL did the statistical analysis and drafted the report. YH, GZ, AP, JEM, KMR, EBR, FBH, and QS contributed to data acquisition or data interpretation and critical review of the report.

Declaration of interests

We declare no competing interests.

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