The Association between Smoking Cessation and HbA1c Control of Type 2 Diabetes Mellitus: A THIN database cohort study

Deborah Lycett (PhD)[1] Linda Nichols (PhD)[2], Ronan Ryan (PhD)[2], Amanda Farley (PhD)[2], Andrea Roalfe (MSc)[2], Mohammed Mohammed (PhD)[3], Lisa Szatkowski (PhD)[4], Tim Coleman (MD)[5], Richard Morris (PhD)[6], Andrew Farmer (MD)[7], Paul Aveyard (PhD)[7].

[1]Coventry University, Faculty of Health and Life Sciences, Priory Street, Coventry, CV1 5FB, UK
[2]University of Birmingham, School of Health and Population Sciences, Birmingham, B15 2TT, UK
[3]University of Bradford, University of Bradford, Richmond Road, Bradford, BD7 1DP, UK
[4]University of Nottingham, University of Nottingham, School of Medicine, Division of Epidemiology and Public Health, Clinical Sciences Building, Nottingham City Hospital, Nottingham, NG5 9PX
[5] University of Nottingham, School of Medicine, Division of Primary Care, D1411, Medical School, Queen's Medical Centre, Nottingham, NG7 2UH
[6]University of Bristol, School of Social and Community Medicine, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, UK
[7]University of Oxford, Nuffield Department of Primary Care Health Sciences, New Radcliffe House Radcliffe Observatory Quarter, Woodstock Road, Oxford, OX2 6GG, UK

Corresponding author: Dr Deborah Lycett, Deborah.lycett@coventry.ac.uk, +44 247 679 5938

ABSTRACT

Background

Smoking increases the risk of developing type-2 diabetes mellitus (T2DM). However several population studies show a higher risk for 3-5 years after smoking cessation than in continuing smokers. After 10-12 years the risk equates to that of never-smokers. Small cohort studies suggest diabetes control deteriorates temporarily during the first year after quitting.

We examined whether or not quitting was associated with altered diabetes control in a population study, for how long this association persisted, and whether or not this association was mediated by weight change.

Methods

A retrospective cohort study (1st Jan 2005 to 31st Dec 2010) of adult smokers with T2DM using The Health Improvement Network (THIN), a large UK primary care database.

We developed adjusted multilevel regression models to investigate association between a quit event, smoking abstinence duration, change in HbA1c and the mediating effect of weight change.

Findings

10,692 adult smokers with T2DM were included. 3,131 (29%) quit smoking and remained abstinent for at least one year. After adjustment for potential confounders, HbA1c increased by 2.3mmol/l (95% CI 1.91to 2.77, $p<0.001$) after quitting. HbA1c decreased as abstinence continued and became comparable to that of continual smokers after 3 years. This increase in HbA1c was not mediated by weight change.

Interpretation

In T2DM smoking cessation is associated with deterioration in glycaemic control, lasting 3 years, and unrelated to weight gain. At a population level, this temporary rise could increase microvascular complications.

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BACKGROUND

Systematic review evidence from 25 prospective cohort studies (1.2million participants) shows smoking is associated with a 44% increased risk of developing type 2 diabetes mellitus (T2DM) (RR 1.44 (95% CI 1.31-1.58))[1]. There is a dose-response relationship; those who smoke more have a higher relative risk than those who smoke less. However, potential confounding by unhealthy behaviours that co-occur with smoking such as poor diet, high alcohol intake and physical inactivity means that causality cannot be assumed.

It seems logical that if smoking increases the risk of developing diabetes that stopping smoking might reduce it. However, epidemiological evidence suggests the reverse, at least in the short-term. Two cross-sectional [2-3] and 6 prospective studies [3-8] have shown the risk of developing diabetes is 14 to 54% higher in the first few years after stopping smoking than in continuing smokers. After 10 to 20 years the risk reduces and is similar to never-smokers. The early elevated risk is partially explained by weight gain in some [3,4,6], but not all[8], of these studies. Two of the studies also reported that the risk of developing diabetes was lower after smoking cessation, in those who smoked fewer cigarettes than those who smoked more heavily [7-8].

It is therefore possible that smoking cessation has a temporary negative impact on glycaemic control. A small study of 25 Japanese smokers with T2DM who were attempting to quit showed a deterioration in HbA1c (mean increase of 0.87%) in those who successfully quit compared to those who continued to smoke. The worsening HbA1c persisted for 12 months after smoking cessation and was unrelated to weight gain during this time[9].

Smoking cessation may therefore present a time when closer monitoring of diabetes, adjustment of anti-diabetic medications to maintain effective glycaemic control, or intervention programmes to prevent diabetes should be implemented. We therefore investigated the association between smoking cessation and glycaemic control in a large retrospective cohort study, this has not been done before.

METHOD

Data source

We used The Health Improvement Network (THIN) database, which contains the electronic medical records (EMRs) of patients from 546 UK primary care practices. This covers over 3.5 million currently-registered patients, and over 10 million patients in total. These patients are representative of the UK population by age, gender, medical conditions and death rates [10]. Records are constantly updated and can be followed over time.

UK General Practitioners (GPs) are paid in part for their performance in caring for patients with diabetes in a system known as the Quality and Outcomes Framework (QOF). Since the QOF in 2004, remuneration of GPs for regularly checking smoking status has meant the recording of smoking status has improved dramatically [11]. Currently, the QOF requires assessment of smoking status (with advice to quit), weight measurement and recording HbA1c to be part of an annual diabetes review. Remuneration is also received for the proportion of patients with an HbA1c below 59mmol/mol.

THIN contains approximately 600,000 patients with a Read code or prescribed drug code indicating diabetes. It therefore offers a data set where it is possible to investigate the association between smoking cessation and glycaemic control in a large sample of patients with diabetes.

Inclusion criteria for practices

We used THIN practices that were collecting data for at least one year before the study start date and were recording mortality to an acceptable standard (their Acceptable Mortality Reporting (AMR) date was before the start of the study).

Inclusion criteria for patients

We included all adult patients (aged ≥18 y), registered with their practice for at least one year on 1st January 2005, with a diagnosis of T2DM prior to 2005. Diabetes type was taken as the first diabetes-type-specific code recorded. Our cohort only included those whose last recorded smoking status before 2005 indicated current smoking, using a previously-validated algorithm[12].

Exclusion criteria for patients

We excluded patients who had a Read code indicating they had gestational diabetes at the study start date, or had a Read code indicating they had non-type1/type2 diabetes at any stage before the study started. We also excluded patients with no recorded HbA1c measurements before the study start date.

The selection criteria for patients was applied in a stepwise process of exclusion (Figure 1).

The cohort began on 1st January 2005. Patients remained in the cohort and were followed-up until transfer out of practice, death or until the end of follow-up (31st December 2010).

Data extraction

For each patient, we extracted data on the outcome of HbA1c, the exposure of smoking status, and potential confounders of age, gender, ethnic group, quintile of the Townsend Index[13] of deprivation, baseline weight, duration of diabetes, diabetes treatment stage, prescription of a statin and QOF season. We extracted data on the potentially mediating variable: time varying weight. These items were extracted from the start of their registration, or the date on which their practice joined THIN and passed their AMR date, until they left the cohort.

HbA1c and weights were identified using THIN Additional Health Data (AHD) codes. Drug prescriptions were identified using Multilex drug codes linked to the British National Formulary (BNF). (Code lists are available from authors on request).

Measurement of variables

<u>Quit period and smoking pattern</u>
For descriptive purposes, the cohort was categorised into three groups 'continual smokers', 'long-term quitters' and 'relapsers', based on recorded changes in smoking status during the cohort follow-up. Continual smokers were identified as smoking at the start of the cohort with no recorded change in smoking status during follow-up. Long-term quitters had a quit event and remained abstinent for one year or longer, and Relapsers had a quit event but all their periods of abstinence lasted less than one year. In modelling, however, we allowed smoking status to vary over time and used the date a change in smoking status was recorded by the practice as an approximate date of actual change in smoking behaviour. The limitation of this assumption is discussed later.

<u>HbA1c</u>
For each patient all HbA1c readings during follow-up were extracted and clinically implausible values were excluded (HbA1c >195mmol/mol). HbA1c was the primary outcome and so all other variables in the model were extracted at, or extrapolated from the value nearest to, the time of each HbA1c reading.

Time since quit
Time since quit was the duration of the longest time of abstinence that lasted at least one year.

Age
Age on 1st January 2005 was extracted in quintiles: under or equal to 52 years, 53 to 59 years, 60 to 65 years, 66 to 73 years and over 73 years.

Socio-economic deprivation (Townsend quintile)
Quintiles of Townsend Index were based on the lower level output area from the 2001 Census (approximately 150 households) in which the patient's home postcode lay. A scale of 1 to 5 was used, 1 was the least deprived, and 5 the most deprived.

Duration of diabetes
This was the length of time between the date of first recording of diabetes or first anti-diabetic drug prescription (whichever was earlier) and 1st January 2005. Categories were: less than 1 year, 1 to 4 years, 5 to 10 years and over 10 years.

Diabetes treatment stage
Four stages of diabetes treatment were defined based on the UK treatment algorithm for glycaemic control in type 2 diabetes[14]. The date of initiation of treatment was carried forward by 6 months to allow HbA1c levels to stabilise in response to treatment adjustments.

Baseline weight (centred around the mean)
This was the first recording of weight (kg) after 1st January 2005.

Weight (time-varying)
This was mean-centred weight (kg) extracted or imputed (see below) at the time of each HbA1c measurement.

Statin
Statin use was recorded as a binary variable. Any potential effect of a statin on HbA1c was considered to occur at the time of first prescribing, when effects are most dramatic, and continue until end of follow-up.

QOF season
A binary variable for QOF season indicated whether HbA1c measurement was recorded in the period leading up to annual QOF return (three months up to 31st March). The model was adjusted for QOF season in order to assess whether HbA1C changed due to closer monitoring in the period before QOF submission.

Imputation of weight

If weight was not recorded at the time of measurement of HbA1c it was necessary to estimate weight for all HbA1c measurements to be included in a model. This imputation was carried out using a multiple regression model to predict weight using time and time-squared (to add curvature to the weight trajectory over time) as explanatory variables. A separate linear regression model was created for each subject in the cohort and the models used weight data from 1st January 2000 to give additional data points. Weights were not imputed if an individual had fewer than three weights recorded, nor were predicted weights extrapolated beyond the time of the observed measurements. We investigated the effect of this imputation by developing a model to predict weight using time and smoking status variables, using both observed and imputed weights. A sensitivity analysis was performed by comparing model estimates when only observed weights were used in the model. We found no important difference between results from these two models.

Description of models

Multilevel regression models

A multilevel regression model was developed to investigate the association between HbA1c, a quit event and duration of smoking abstinence. The model allowed each person to have their own slope and intercept for the trajectory of HbA1c over time. In addition, a random effect for each GP practice was included to reflect the hierarchical nature of the data and to produce within-practice estimates of effect.

Multilevel models can incorporate time-invariant and time-varying potential confounding variables. Time-invariant covariates included were: gender, age quintile, Townsend quintile, diabetes duration and baseline weight. Time-varying covariates were: time, time since quit event, whether a quit occurred, diabetes treatment stage, weight (time-varying), statin prescription and QOF season. Time-varying covariates allowed changes in these variables to occur throughout the duration of the cohort so that all changes in status over time were included in the model. Time since quit was modelled with both linear and quadratic terms in order to allow for curvature in the HbA1c trajectory after quitting. Higher order polynomials were tried but were removed as they did not improve the model fit significantly when we used likelihood ratio tests, to compare nested models ($p>0.05$).

Model 1 investigated the relationship between HbA1c and smoking patterns without adjustment for potential confounding variables. Model 2 adjusted for all potential confounding variables above with the exception of time-varying weight. Model 3 additionally adjusted for time-varying weight to investigate whether weight change mediated change in HbA1c after a quit.

To assess whether the inclusion of Relapsers, whose smoking profile included short periods of abstinence, would influence model estimates a sensitivity analysis was carried out which included only Continual Smokers and Long-Term Quitters.

Trajectory of HbA1c using multi-level regression model

We plotted predicted HbA1c values for a patient who continued to smoke and a patient who quit in the first year and remained abstinent. For ease of comparison these plots were for a male, aged 60 – 65years, with Townsend score 3, diabetes duration of 1-5 years, treated with diet, lifestyle plus metformin and prescribed a statin. All time-varying covariates remained constant and only fixed effects were included in the predicted values.

Local polynomial regression plots

From the observed HbA1c data we created local polynomial regression plots for both Continual Smokers and Long-Term Quitters. We performed kernel-weighted local polynomial regressions of HbA1c on time and displayed graphs of the smoothed values with confidence bands. For quitters, the point at which they quit is represented by time=0, so the effect of a quit on HbA1c can be seen for all patients regardless of when their quit occurred. Visual inspection of normal probability plots and histograms of residuals were used to check model assumptions. All statistical analyses were performed using Stata 12.

Ethical Approval

THIN Data Collection Scheme was approved by the South-East Multicentre Research Ethics Committee (SE-MREC).

Role of the Funding Source

This study was funded by the National Institute for Health Research (NIHR) School for Primary Care Research (SPCR). This report presents independent research funded NIHR. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. DL as corresponding author had full access to the data and final responsibility for the decision to submit for publication.

RESULTS

157,691 patients were assessed for eligibility. There were 12030 people with T2DM who were current smokers on 1st January 2005. Not all these patients had HbA1c recorded so 10,692 patients were available for the multilevel model. Around half of these, 5,831 (55%), did not make a quit attempt in the follow-up period. Of the remainder, 3,131 (29% of total cohort) made at least one quit of one year or longer (Figure 1).

1338 patients were excluded from the analysis because they had no HbA1c after 1/1/2005, had insufficient weight data, or because they had no Townsend score. They were broadly similar to those who were included in the analysis in terms of gender (57% and 60% male, respectively), age (median (IQR) 66 (57-65) years and 62 (54-70) years, respectively) and where Townsend deprivation quintile was known. Where ethnic group was known, higher proportions were from black and minority ethnic groups (29% and 8%, respectively). The duration of diabetes was a mean (SD) one year longer in those who were excluded (7.3 (6.6) and 6.1 (5.8) years, respectively), but the proportion of patients at each treatment stage were similar. Patients included in the analysis had a median follow-up period twice that of those excluded (6.0 and 2.5 years, respectively): when patients without a Townsend score were removed, the median follow-up period for those excluded dropped further, from 2.5 to 1.4 years (Table 1a).

Baseline patient demographics were similar for the three smoking pattern groups (Table 1b).

There was an increase in HbA1c of 2.30mmol/mol (95% CI: 1.87-2.72) after quitting (Model 1, table 2). Adjusting for age, gender, Townsend quintile, diabetes duration, treatment stage, baseline weight, statin prescription and QOF season (Model 2, table 2) did not significantly change the association between HbA1c and quitting (2.34mmol/mol, 95% CI: 1.91-2.77). Further adjustment for time-varying weight (Model 3, table 2)) did significantly not alter the association between HbA1c and quitting (2.29mmol/mol (95% CI: 1.86-2.72)). Time-varying weight was associated with deterioration in glycaemic control after cessation (0.09mmol/mol increase in HbA1c for a 1kg increase in weight) however a rise of 0.09mmol/mol per kg would have a clinically negligible effect on HbA1c for most quitters as the mean weight gain is 5kg in the first year following cessation.

The effect of short-term abstinence from smoking (quitting for less than one year i.e. Relapsers) was not modelled in the current analysis, therefore the trajectory of HbA1c for a Relapser is assumed to be the same as that of a Continual Smoker. To determine whether the presence of patients who quit for short periods might influence the model estimates, a sensitivity analysis which excluded these patients was performed and did not alter the findings (Table 3).

In Long-Term Quitters HbA1c rose at the time of quitting and decreased gradually as abstinence continued (Figure 2 & Figure 3(web appendix)). In Continual Smokers HbA1c rose gradually over time (Figures 2 & Figure 3 (web appendix)). HbA1c in quitters became comparable to the levels seen in Continual Smokers by 3 years post-quit (Figure 2 & Figure 3(web appendix)).

The polynomial models show HbA1c began to rise before the time of quit. This is likely to be an effect of using date of recording a change in smoking status as a proxy for quit date; the actual quit date must have occurred prior to attending the practice in order for the clinical team to record that the patient has stopped smoking. .

DISCUSSION

In those with T2DM, quitting smoking was associated with a transient 2.29mmol/mol rise in HbA1c, which gradually reduced but remained elevated beyond the trajectory of Continual Smokers during the first three years of abstinence. This change in HbA1c was unexplained by change in weight associated with smoking cessation.

This was a large study of UK primary care patients with T2DM who smoke. THIN database has stringent checks in place on the recording of accurate patient data. In addition we used the timeframe where recording of smoking status and annual diabetes reviews is maximised by QOF incentives. We also used a validated algorithm[12] to minimise inaccuracies of recording of smoking status.

Our findings were robust to adjustment for potential confounders, and to sensitivity analysis whereby we checked the influence of short versus long-term quits, and visually inspected observed versus predicted trajectories of HbA1c.

We also considered the possibility that the rise in HbA1c associated with quitting, that was not seen in Continual Smokers, was due to a difference in prescription or titration of glucose lowering medication over time between these groups. However, more quitters than Continual Smokers/Relapsers commenced sulfonyureas (31% vs 15% respectively) and, among the quitters, a larger proportion commenced insulin therapy compared with Continual Smokers/Relapsers (85% vs 65% respectively). Therefore the data on prescribing alongside that for glycaemic control indicates that glucose lowering treatment for the quitters was intensified after quitting, with between a third and a half more patients progressing to more intensive treatment. This would suggest that the effect on glucose control in quitters is not caused by changes in medication and that the observed difference between quitters and Continual Smokers of around 2.3mmol/mol may have been considerably greater if medication adjustment had not taken place.

Our data are nonetheless limited by the accuracy of the information available within the THIN database. We used the date of quitting smoking as the date that a quit was recorded in the patient notes. It is almost certain that the quit would have commenced earlier than the date of recording at the practice. However this is likely to lead to a systematic underestimation of the association between quitting and HbA1c and would not nullify the results we found.

Eleven percent of our cohort had missing data such that they were excluded from the analysis. These 1338 patients were excluded for reasons that were unlikely to be related to their clinical characteristics. The majority of the patients excluded from the analysis (615/1338) had a missing Townsend quintile. This happens when the linkage process between patient postcode and deprivation score was not carried out at a particular practice, and when the postcode recorded for an individual patient by their practice is not known or invalid. There may be occasions, however, when a patient of no fixed abode registers with a general practice: they may be assigned a dummy address by the practice, but this is likely to be a rare event. The principal characteristic of the remaining excluded patients who had a Townsend quintile, but had no HbA1c or had insufficient weight values to be included in the analysis (723/1338) was that they had a median follow-up of just 1.4 years (IQR 0.6 – 3.1). Routine care of patients with diabetes in UK general practice includes a review

every 12 to 18 months: these are the occasions when weight and HbA1c are likely to be recorded and available for later analysis by researchers. It is not surprising, therefore, that this group of patients were excluded from the analysis: their duration of follow-up was too short to have multiple occasions on which the data of interest were recorded. Our findings are therefore perhaps most generalizable to those who regularly engage with follow-up. It may be reasonable to consider that those who do not engage in follow-up are less likely to have good glycaemic control, however this does not appear to be the case as an equal proportion of included and excluded patients were in the same phase of treatment. There is nothing to suggest their glycaemic response to quitting smoking would be any different to those included, or nullify the association we found.

It was unexpected that the rise in HbA1c that occurred after quitting was not mediated by weight gain. As expected, people who stopped smoking gained weight, with a mean increase of 4.68kg (95% CI: 2.21-7.14) in those who quit in the long term. This is consistent with a mean weight gain of 5kg associated with smoking cessation found in a systematic review of cohort studies[15], suggesting that this cohort were not unusual in their experience of weight gain after cessation. One other possible explanation could be that we imputed weight where it was not measured at the same time as HbA1c. Only 21% of HbA1c readings had weight recorded simultaneously; therefore it was necessary to impute weight. We used a single imputation method, however analyses unadjusted for weight (Model 1, table 2) and sensitivity analyses to assess the impact of weight imputation, gave similar estimates of change in HbA1c at the time of quit and do not suggest imputed weight caused undue influence on our results. The imputation we used to estimate weight did not include a random error, which may have led to regression dilution so that the relationship we found between HbA1c and weight may have been underestimated. We checked the influence of this imputation by excluding imputed weights and rerunning the model and this gave similar results. We also checked our weight change data as an outcome according to smoking status. While this adds to the suggestion that a mechanism other than weight gain was responsible for the rise in HbA1c we cannot be sure.

Our analyses do not account for any changes in dietary or physical activity that may have occurred after stopping smoking that perhaps explain why HbA1c rose. However for physical activity to explain our findings physical activity would have to decrease with smoking cessation and has not been shown to be the case[16]. Rather than dietary change being a confounder, measurement of this may offer an explanation as evidence suggests dietary energy intake and weight increases with smoking cessation[16, 17]. While we did not find an increase in body weight explained our association (although we cannot rule this out due to the possibility of regression dilution) it is possible that regardless of weight change, change in dietary composition was responsible. There is some evidence of an increased preference for sweet taste post-cessation[18] this may result in an increase in dietary glycaemic load and thus explain the association we found. We know from a systematic review of randomised controlled trials that low versus high glycaemic load diets improve glycaemic control in type 2 diabetes[19]. However studies investigating dietary glycaemic load during smoking cessation are needed to confirm this.

There is also the possibility of residual confounding from variables such as diabetes treatment stage and statin use, since these categories did not include the medication dosages. Although the biggest impact of medication on glycaemic control is likely to occur with the addition of new drug, which we adjusted for, rather than dosage increase.

We are only able to show a temporal association between quitting smoking and rising HbA1c and we cannot assume that it was giving up smoking that caused the rise. It is possible that a common cause accounted for both. For example, illness could both worsen glycaemic control and prompt quitting. Many people who smoke stop smoking after an acute coronary event, for example. However, such events are likely to prompt renewed

vigilance from both patients and clinicians and improve glycaemic control and we know of no evidence that glycaemic control worsens with the onset of smoking-related illness.

The association we have found between quitting smoking and HbA1c in those with T2DM is consistent with findings, from a small cohort study, by Iino et al, 2004[11] who found HbA1c increased by a mean(SD) 0.87(0.4)% following a quit attempt and remained high at 1 year follow-up. Iino et al also found no evidence that this was mediated by change in weight associated with smoking cessation.

We are unaware of any other studies which have investigated the association between HbA1c and a quit event in those with diabetes. However, as discussed previously, several large prospective studies show consistently that in those without diabetes there is an increased risk of developing diabetes in the first 3-5 years following smoking cessation compared with continuing to smoke[3-8]. There is inconsistent evidence that this risk is mediated either fully or partially by cessation-related weight gain[3,4,6,8]. It may be that irrespective of weight gain, dietary preferences for sweeter food[18] leads to a diet with a higher glycaemic load resulting in a higher glycaemic response. It may alternatively be that there is some heightened insulin resistance in the first few years post-cessation, but short-term studies, at least, suggest the opposite[20].

Our findings suggest that smoking cessation is associated with deterioration in glycaemic control and provides evidence that this may continue for three years. Although at the level of an individual patient, a change in HbA1c of 2.29mmol/mol (0.21% points[21]) may not be considered clinically important, this may lead to increased risk of microvascular complications on a population level. We know that for every 1% unit increase in HbA1c there is a 37% increase in microvascular complications and a 15% increase in myocardial infarction (MI)[22], so the increase seen here are equivalent to a 8% increase in microvascular complications and a 3% increased risk of MI. We do not know how important a temporary rise, over a period of a few years, is on the development of these complications. Nonetheless, there is clear evidence that stopping smoking reduces the risk of MI[23] despite this apparent worsening of glycaemic control. A study by Clair et al (2013)[24] found from 25year follow-up of the Framingham offspring cohort that cardiovascular events in those with diabetes were approximately 50% less likely to occur in recent quitters (<4 years) (HR (95% CI) 0.49 (0.11, 2.19)), long term quitters (>4years) (0.57 (0.28, 1.15)) and non-smokers (0.49 (0.22, 1.09)) in comparison to smokers. Thus the benefits of stopping smoking on reducing cardiovascular disease are not outweighed by the rise in glycaemia and we continue to advocate that those with diabetes should quit smoking, consistent with clinical guidelines [14,25]. Nonetheless optimising blood pressure and statin treatment prior to smoking cessation may be a prudent way to maximise the benefits of cessation given the rise in HbA1c that seems to occur.

This study has shown strong evidence that glycaemic control worsens after cessation and that this does not appear to be primarily down to increases in weight that usually follow cessation. This highlights the need for proactive review of glycaemic control and prompt adjustment of medication in this patient group both prior to and following smoking cessation.

Conflict of Interest Statement

Dr. Lycett, Dr. Ryan, Dr. Farley, Dr. Szatkowski, Dr Morris, Dr Coleman and Mrs Roalfe report grants from NIHR SPCR, during the conduct of the study; Dr. Coleman also reports personal fees from Pierre Fabre Laboratories, outside the submitted work; Dr. Aveyard reports grants from UK Centre for Tobacco and Alcohol Studies (UKCRC), grants from NIHR School for Primary Care Research, during the conduct of the study; personal fees from Pfizer, personal fees from McNeil, outside the submitted work; Dr. Nichols has nothing to disclose.

Figure 1. CONSORT Flow Diagram from eligible patients to analysis

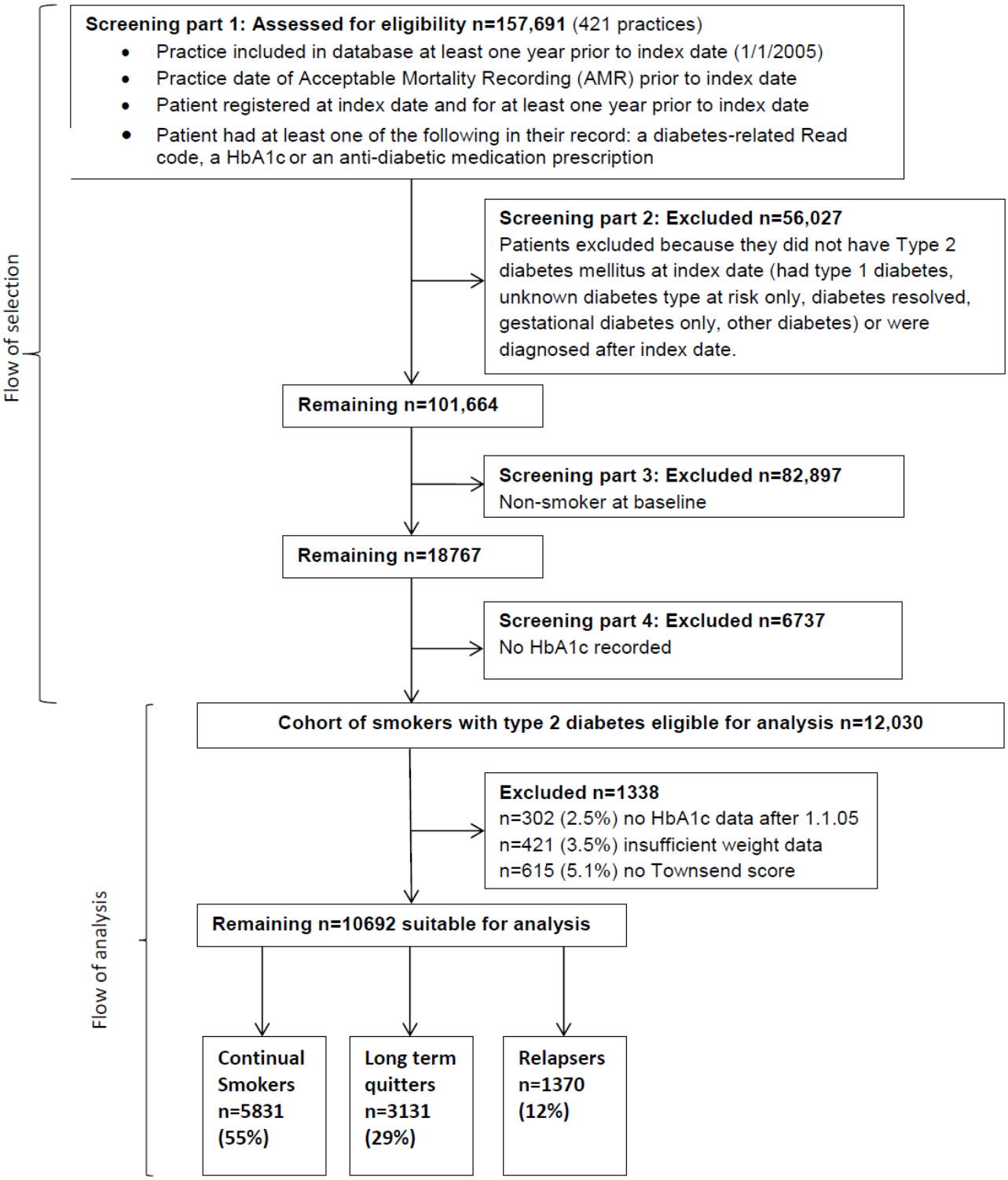


Table 1a: Characteristics of patients included and excluded from analysis

	Included	Excluded
Number of patients	**10,692**	**1,338**
Gender		
Male	6,435 (60.2%)	768 (57.4%)
Female	4,257 (39.8%)	570 (42.6%)
Age at start of study (years)		
Mean (SD)	61.6 (11.8)	64.5 (13.9)
Median (IQR)	62 (54 - 70)	66 (56-75)
Ethnic group (% of known)		
White	4,002 (92.4%)	210 (70.7%)
Black	71 (1.6%)	24 (8.1%)
Asian	196 (4.5%)	45 (15.2%)
Mixed	14 (0.3%)	6 (2.0%)
Chinese	6 (0.1%)	2 (0.7%)
Other	44 (1.0%)	10 (3.4%)
Not known	6,359	1,041
Townsend deprivation index quintile (% of known)		
1 (least deprived)	1,521 (14.2%)	91 (12.6%)
2	1,844 (17.3%)	126 (17.4%)
3	2,349 (22.0%)	148 (20.5%)
4	2,642 (24.7%)	175 (24.2%)
5 (most deprived)	2,336 (21.9%)	183 (25.31%)
Not known	0	615
Duration of diabetes (years)		
Mean (SD)	6.1 (5.8)	7.3 (6.6)
Median (IQR)	4.3 (2.0 – 8.5)	5.6 (2.6 – 10.7)
Diabetes treatment stage at start of study (lagged)		
Diet & lifestyle	3,004 (28.1%)	370 (27.7%)
+ metformin	3,578 (33.5%)	472 (35.3%)
+ sulfonylureas	2,576 (24.1%)	305 (22.8%)
+ TZDs OR Insulin OR GLP-1 analogs/DPP-4 inhibitors	1,534 (14.4%)	191 (14.3%)
Duration of follow-up (years)		
Median (IQR)	6.0 (4.8 – 6.0)	2.5 (1.0 – 4.5)
Median (IQR) if Townsend missing	n/a	1.4 (0.6 – 3.1)

SD: Standard deviation

IQR: Interquartile Range

TZDs: Thiazolidinediones

GLP-1: Glucagon-like peptide-1

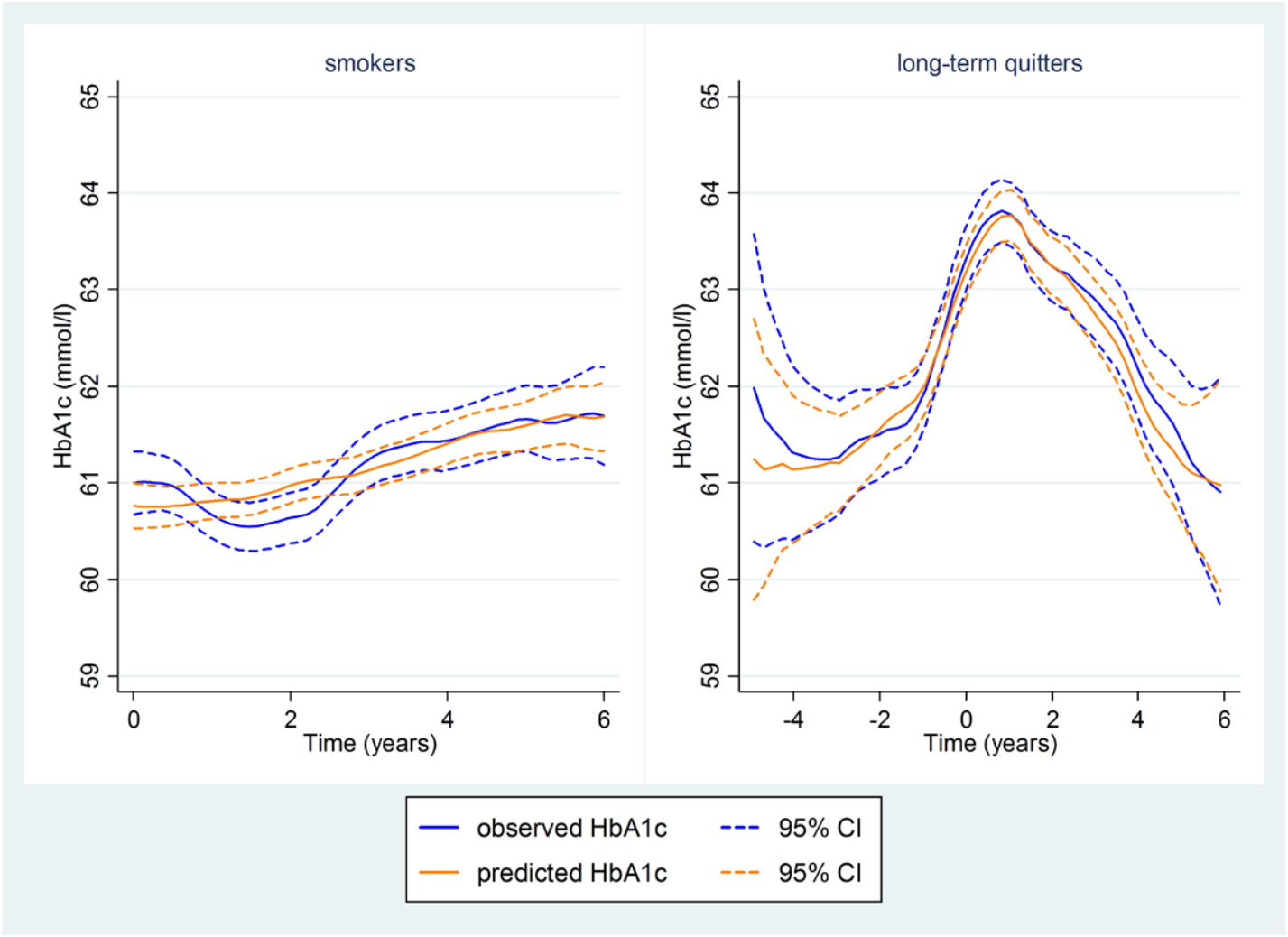
DPP4: Dipeptidyl peptidase-4

Table 2b: Patient characteristics by smoking pattern

	Continual smokers	Long-term quitters (at least one quit ≥ 1 year)	Relapsers (all quit attempts < 1 year)
Gender			
Male	3,407 (58.4%)	2,017 (64.4%)	1,011 (58.4%)
Female	2,424 (41.6%)	1,111(35.6%)	719 (41.6%)
Age at start of study (years)			
Mean (SD)	61.6 (12.1)	61.6 (11.3)	61.6 (11.8)
Median (IQR)	62 (54 - 70)	62 (54 - 70)	62 (54 - 70)
Ethnic group			
White	2,054 (35.2%)	1,284 (41.0%)	664 (38.4%)
Black	22 (0.4%)	31 (1.0%)	18 (1.0%)
Asian	89 (1.5%)	79 (2.5%)	28 (1.6%)
Mixed	7 (0.1%)	6 (0.2%)	1 (0.1%)
Chinese	6 (0.1%)	0	0
Other	15 (0.3%)	17 (0.5%)	12 (0.7%)
Not known	3,638 (62.4%)	1,714 (54.7%)	1,007 (58.2%)
Townsend deprivation index quintile			
1 (least deprived)	747 (12.8%)	529 (16.9%)	245 (14.2%)
2	985 (16.9%)	583 (18.6%)	276 (16.0%)
3	1,278 (21.9%)	707 (22.6%)	364 (21.0%)
4	1,466 (25.1%)	734 (23.4%)	442 (25.6%)
5 (most deprived)	1,355 (23.2%)	578 (18.5%)	403 (23.3%)
Duration of diabetes (years)			
Mean (SD)	6.1 (5.9)	6.2 (5.8)	6.1 (5.8)
Median (IQR)	4.3 (2.0 - 8.5)	4.4 (2.0 - 8.7)	4.2 (2.0 – 8.4)
Diabetes treatment stage at start of study (lagged)			
Diet & lifestyle	1,669 (28.6%)	858 (27.4%)	477 (27.6%)
+ metformin	2,019 (34.6%)	1,001 (32.0%)	558 (32.3%)
+ sulfonylureas	1,372 (23.5%)	772 (24.7%)	431 (24.9%)
+ TZDs OR Insulin OR GLP-1 analogs/DPP-4 inhibitors	771 (13.2%)	499 (16.0%)	264 (15.3%)
Number of HbA1c readings per patient			
Median (IQR)	8 (5 – 11)	10 (7 – 13)	9 (6 – 12)
Number of HbA1c readings per patient in QoF period			
Median (IQR)	2 (1 - 3)	3 (1 - 4)	2 (1 - 4)
HbA1c (mmol/mol): all readings			
Mean (SD)	61.1 (18.1)	62.7 (17.9)	61.6 (17.7)
Median (IQR)	57.4 (48.6 – 69.4)	58.5 (49.7 – 71.6)	57.4 (49.7 – 70.5)
Change in HbA1c (end – start)			
Mean (SD)	-1.0 (18.5)	0.4 (19.3)	-0.3 (17.9)
Median (IQR)	-1.1 (-9.8 – 6.6)	0 (-9.8 -9.8)	0 (-9.8 – 7.7)
HbA1c: SD between practice	2.3	3.1	2.0
HbA1c: SD between patients	15.0	13.9	14.5
HbA1c: SD within patient	11.0	11.6	10.8
ICC: practice level	0.02	0.03	0.01
ICC: patient level	0.66	0.60	0.65
Duration of follow-up (years)			
Median (IQR)	6.0 (4.1 – 6.0)	6.0 (6.0 – 6.0)	6.0 (4.8 – 6.0)
Duration of long-term quit (years)			
Median (IQR)	-	2.8 (1.7 – 4.4)	-
Weight (Kg) (including imputed weights)			
Mean (SD)	85.0 (19.6)	90.0 (20.2)	86.7 (20.2)
Median (IQR)	83.1 (71.5 – 96.7)	88.0 (76.1 – 101.6)	84.0 (72.8 – 98.8)
Change in weight (end-start)			
Mean (SD)	-1.2 (7.3)	1.7 (8.6)	-0.8 (7.6)
Median (IQR)	-1.0 (-5.1 – 2.7)	1.6 (-2.8 – 6.4)	-0.8 (-4.8 – 3.1)
Number (%) of patients prescribed a statin	4,749 (81.4%)	2,680 (85.6%)	1,498 (86.6%)
Total	**5,831**	**3,131**	**1,730**

SD: Standard deviation, IQR: Interquartile Range, TZDs = Thiazolidinediones, GLP-1 = Glucagon-like peptide-1, DPP-4 = Dipeptidyl peptidase-4 , ICC=Intraclass Correlation Coefficient

Figure 2. Observed and predicted HbA1c in Continual Smokers and Long-Term quitters*



*This figure was not created by the models 1 to 3, they were created from the observed HbA1c data using local polynomial regression. We performed kernel-weighted local polynomial regressions of HbA1C on time and displayed graphs of the smoothed values with confidence bands. For quitters, the point at which they quit is represented by time=0, so the effect of a quit on HbA1c can be seen for all patients regardless of when their quit occurred

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