Incidence and characteristics of remission of type 2 diabetes in England: A cohort study using the National Diabetes Audit

Short title: Incidence of remission of type 2 diabetes

Naomi Holman PhD[1], Sarah H Wild PhD[2], Kamlesh Khunti MD[3], Peter Knighton MPhys[4], Jackie O'Keefe MSc[4], Chirag Bakhai MBA[5], Bob Young MD[6], Naveed Sattar FMedSci[1], Jonathan Valabhji MD[5,7,8], Edward W Gregg PhD[9]

[1] Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[2] Usher Institute, College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK
[3] Diabetes Research Centre, University of Leicester, Leicester, UK
[4] Analytical Services – Population Health, Clinical Audit and Specialist Care, NHS Digital, Leeds, UK
[5] NHS England and Improvement
[6] Diabetes UK, London, UK
[7] Department of Diabetes and Endocrinology, St Mary's Hospital, Imperial College Healthcare NHS Trust, London, UK
[8] Division of Metabolism, Digestion and Reproduction, Imperial College London, London, UK
[9] School of Public Health, Imperial College London, London, UK

Abstract word count: 250
Word count: 4553
Tables: 1
Figures: 2
Supplementary tables: 3
Supplementary figures: 1
Key words: type 2 diabetes, remission

Corresponding author:
Naomi Holman
c/o RC214 Level C2, Institute of Cardiovascular & Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom
Tel: 07986563124
Email: naomi.holman@glasgow.ac.uk

Abstract

Objective: To assess the incidence of remission of type 2 diabetes in routine care settings.

Research design and methods: People with type 2 diabetes (HbA1c ≥48 mmol/mol (6·5%) or <48 mmol/mol (6·5%) with a prescription for glucose lowering medications) alive on 1st April 2018 were identified from a national collation of health records in England and followed until 31st December 2019. Remission was defined as two HbA1c measurements <48 mmol/mol at least 182 days apart, with no prescription for glucose lowering medications 90 days prior to these measurements.

Results: In 2,297,700 people with type 2 diabetes the overall incidence of remission per 1000 person-years was 9·7 (95% CI 9·6-9·8), and 44·9 (95% CI 44·0-45·7) in 75,610 (3.3%) people who were diagnosed less than a year. In addition to shorter duration of diagnosis, baseline factors associated with higher odds of remission were no prescription for glucose lowering medication, lower HbA1c and BMI, BMI reduction, White ethnicity, female sex and lower socio-economic deprivation. Among 8940 (0.4%) with characteristics associated with remission (diagnosed less than two years, HbA1c <53 mmol/mol, prescribed metformin alone or no glucose lowering medications, BMI reduction of ≥10%) incidence of remission was 83·2 (95% CI 78·7-87·9) per 1000 person-years.

Conclusions: Remission of type 2 diabetes was generally infrequent in routine care settings but may be a reasonable goal for a subset of people who loose significant weight shortly after diagnosis. Policies that encourage intentional remission of type 2 diabetes should seek to reduce the ethnic and socioeconomic inequalities identified.

Introduction

The prevalence of diagnosed and undiagnosed diabetes in adults in England is estimated to be 8·6% and is projected to rise to 9·7% by 2035.[1] Type 2 diabetes accounts for 90 to 95% of people with diabetes.[2] Historically type 2 diabetes was considered to be a lifelong progressive condition but there is now clear evidence that remission of type 2 diabetes is feasible following intensive lifestyle interventions[3–5] or bariatric surgery[6–9]. However, successful lifestyle interventions are of high intensity and have, as yet, unclear long-term sustainability and scalability in the real world setting. Similarly, bariatric surgery is only indicated for a small proportion of people with type 2 diabetes.

We are not aware of any population-based studies that have assessed incidence of remission of type 2 diabetes in routine clinical care and the recent consensus report on the definition and interpretation of remission in type 2 diabetes highlights the need for evidence on the frequency and duration of remission.[10] It remains unclear what the incidence of remission is for people diagnosed with type 2 diabetes in routine care settings. As one of the few national registries of type 2 diabetes, the National Diabetes Audit (NDA) provides an opportunity to quantify the incidence of diabetes remission in routine care. The aim of this study was to determine the incidence of remission over a follow up period of 21 months and determine which characteristics predict remission from type 2 diabetes in the English population.

Methods

Data sources

The NDA has collated data on people with diagnosed diabetes registered with a primary or specialist healthcare provider in England since 2003.[11] Individuals are included if they have a valid diagnostic code for diabetes mellitus (excluding gestational diabetes) in their electronic health record. Demographic and clinical data are extracted from general practice electronic clinical systems using the General Practice Extraction Service (a national centralised data collection service for England). This is supplemented by data submitted by specialist diabetes services. The data collated by the NDA from primary care and specialist services includes all HbA1c measurements and prescriptions for glucose lowering medications. Data from the NDA were linked using unique National Health Service (NHS) number to Hospital Episode Statistics (HES) which records all hospital admissions in England and death registrations collated by the Office for National Statistics. In 2017/18 the NDA collected data from 98·2% of general practices in England.[12]

Study population and observation period

The study population was people with a documented diagnosis of type 2 diabetes registered with a healthcare provider in England and included in the 2017/18 NDA data collection, still alive on 1st April 2018. The cohort was followed to 31st December 2019. Those who did not have a valid HbA1c measurement between 1st April 2017 and 31st March 2018 (n=207,295, 7·3%) were excluded from the cohort. People with a HbA1c measurement between 1st April 2017 and 31st March 2018 less than 48 mmol/mol (6·5%) with no prescriptions for glucose lowering medication over the same period were also excluded from the cohort (339,440, 12·9%), as they may have already been in remission from type 2 diabetes and therefore could not become incident cases over the period of observation. The resulting cohort was people with

type 2 diabetes who did not meet the criteria for remission at the start of the follow up period (1st April 2018), with either a HbA1c of 48 mmol/mol (6·5%) or greater irrespective of prescription for glucose lowering medications or a HbA1c less than 48 mmol/mol (6·5%) and one or more prescription for glucose lowering medications in the 90 days prior to HbA1c measurement at the start of follow-up.

The latest recorded type of diabetes was assumed to be most accurate. Where data for an individual were provided by both primary care and a specialist diabetes service then the type of diabetes identified by the specialist service was assumed to be more accurate than that recorded in primary care.[13] For example, an individual with a diagnostic code for type 2 diabetes in general practice but a code for type 1 diabetes from a specialist provider in the same year would be considered to have type 1 diabetes and excluded from the cohort. People who had a hospital admission for cystic fibrosis (ICD-10 code E84, n=610) between 1st January 2003 and 31st December 2019 and those who had a hospital admission for pancreatic disease (ICD-10 codes K85-6, n=21,165) between 1st January 2003 and date of diagnosis of diabetes were excluded as they may have been inaccurately categorised as having type 2 diabetes. Five individuals whose sex was not recorded as male or female were also excluded.

Outcome

Remission was defined as at least two HbA1c measurements less than 48 mmol/mol (6.5%) at least 26 weeks apart (without any intervening HbA1c measurements of 48 mmol (6.5%) or greater), with no record of prescription for glucose lowering medications between these measurements and at least 90 days prior to each

measurement[14]. The date of remission was taken as the date of the second relevant HbA1c. A sensitivity analysis was undertaken using a single HbA1c measurement less than 48 mmol/mol (6·5%) in the absence of a prescription for glucose lowering medications in the preceding 90 days as the definition of remission. Where people met the criteria for remission of type 2 diabetes, HbA1c measurements after entering remission were grouped into those who continued to meet the criteria for remission and those that were subsequently in the diabetes range (48mmol/mol (6.5%) or greater, 48mmol/mol (6.5%) or less with a prescription for glucose lowering medications in the prior 90 days).

SNOMED codes 703136005 (diabetes mellitus in remission) and 703138006 (type 2 diabetes mellitus in remission) were identified as being 'coded as in remission' In order to assess the number and proportion of people meeting the definition of remission described above who had a record of remission in their records.

Exposures

Age on 31st March 2018 was calculated based on date of birth. Self-reported ethnicity was grouped into White, Mixed, Asian, Black, Other, and missing. Socio-economic deprivation was measured using the Indices of Multiple Deprivation 2019[15] based on the home postcode and stratified into quintiles. Duration of diagnosed diabetes on 31st March 2018 was calculated based on the date of diagnosis recorded in the electronic patient record. The lowest HbA1c and body mass index (BMI) recorded between 1st April 2017 and 31st March 2018 were identified and defined as baseline measurements. For individuals who entered remission, change in BMI was calculated as the difference between baseline BMI and the measurement within 90

days closest to the date of entering remission (the second HbA1c measurement less than 48 mmol/mol (6.5%)). Change in BMI for those people who did not enter remission was calculated as the difference between baseline BMI and the latest measurement prior to 31st December 2019.

NHS hospital admission for co-morbidities associated with unintentional weight loss (heart failure (ICD-10 code I50), cancer (ICD-10 codes C01-C99), chronic obstructive pulmonary disease (COPD) (ICD-10 codes J40-44), and dementia (ICD-10 codes F00-03)) between 1st April 2015 and 31st March 2019 were identified using Hospital Episode Statistics (HES), a database of all NHS hospital activity in England. People who had undergone bariatric surgery in the NHS (see Table S1 for definition) between 1st April 2017 and 31st March 2019 were also identified using HES.

Statistical methods

Remission rates per 1000 person years with confidence intervals were calculated using Byar's method.[16] Person years was calculated as the time from 1st April 2018 to the earliest of: date of remission, date of death, or 31st December 2019. A multivariable logistic regression model was constructed for all individuals in the cohort to calculate the adjusted odd ratios of entering remission associated with age, sex, deprivation, ethnic group, duration of diagnosis, baseline HbA1c, baseline BMI, and change in body mass index. All variables were treated as categorical variables and included a category for missing data, meaning that individuals were not excluded from the regression model due to incomplete data and the potentially different outcomes of those with missing data could be identified. A further multivariable logistic regression model in the sub-group of people with early stage

type 2 diabetes (a baseline HbA1c <53 mmol/mol, duration of diagnosed diabetes of two years or less and prescribed only metformin or no glucose lowering medication at baseline) and no history of heart failure, COPD, cancer, or dementia was performed using the same variables. Statistical significance was defined as p-value <0·05 and confidence intervals (CI) were set at 95%. Statistical calculations were undertaken in SAS Enterprise Guide 7.1.

Information Governance

The legal basis for the NDA data collection and linkage is a Direction from NHS England to NHS Digital according to section 254 of the Health and Social Care Act 2012. All numbers taken from the NDA are rounded to the nearest five to protect confidentiality.

Results

There were 2,297,700 people with type 2 diabetes defined as a baseline HbA1c between 1st April 2007 and 31st March 2018 of 48 mmol/mol (6·5%) or greater or a HbA1c less than 48 mmol/mol (6·5%) with one or more prescription for glucose lowering medications in the 90 days prior to measurement. Of these, 38,530 (1·7%) people met the criteria for remission in the 21 months between 1st April 2018 and 31st December 2019, median follow-up 91 weeks (Table 1). People who entered remission were more likely to be older, female, living in less socioeconomically deprived areas and to be of White ethnicity compared to those who did not meet the criteria for remission. They also had a shorter duration of diagnosis, lower baseline HbA1c, and lower baseline BMI (Table 1) compared to those without remission. Baseline and follow-up BMI was recorded for 1,746,940 (76.0%). Among those

entering remission the mean reduction in BMI from baseline was 2·5% (SD 10·2%) compared to a reduction of 0·2% (SD 8·1%) in people in whom there had been no remission. At cohort entry, 48·6% of people who later entered remission were not prescribed any glucose lowering medication, 40·7% were prescribed metformin only, 10·0% were prescribed other non-insulin glucose lowering medication (+/- metformin) and 0·7% were prescribed insulin.

The incidence of remission was 9·7 (95% CI 9·6-9·8) per 1000 person-years overall. In people with co-morbidities that may induce weight loss, incidence of remission was higher (11·8 (95% CI 11·5-12·0) per 1000 person-years compared to 9·2 (95% CI 9·1-9·3) in those without such a co-morbidity). A history of bariatric surgery in the NHS was rare (0·06% of all people included in the analysis). In those who had bariatric surgery but no co-morbidity that may induce weight loss, the rate of remission was 205·8 (95% CI 183·8-229·8) per 1000 person-years falling to 82·5 (95% CI 61·8-107·9) per 1000 person-years for those with a co-morbidity associated with unintentional weight loss who underwent bariatric surgery.

Overall rates of remission were higher in women, older people, those living in less socioeconomically deprived areas, those from White ethnic groups, and those with a shorter duration of diagnosed diabetes than their respective comparison groups (see Figure 1). For the sub-group of 208,260 (9.1% of the whole cohort) people who had a diagnosis of diabetes for less than two years, a baseline HbA1c of less than 53 mmol/mol (7·0%), were prescribed metformin alone or no glucose lowering drugs and had no history of cancer, heart failure, COPD or dementia, the overall rate of remission was 37·6 (95% CI 37·0-38·3) per 1000 person-years. In a further sub-

group of 8940 (0.4% of the total cohort) people who had a diagnosis of diabetes of less than two years, a baseline HbA1c of less than 53 mmol/mol (7.0%) and who achieved a reduction in body mass index of 10% or more from baseline, the incidence of remission was 83·2 (95% CI 78·7-87·9) per 1000 person-years.

Incidence of remission also varied by medications prescribed at baseline; remission rates were higher amongst people who were not prescribed any glucose lowering medications at baseline (58.4 (95% CI 57·6-59.3) per 1000 person-years) compared to those prescribed metformin alone (11.1 (95% CI 10·9-11·3) per 1000 person-years). In people prescribed non-insulin, non-metformin glucose lowering medications at cohort entry remission was rare and incidence significantly lower (2.0 (95% CI 1.9-2.0) per 1000 person-years), as was the case in those prescribed insulin (1.6 (95% CI 1.4-1.8) per 1000 person-years).

After adjusting for other characteristics, men had lower odds of entering remission than women (OR 0.96 (95% CI 0.94-0.98)), whilst those from all non-White ethnic groups had lower odds of entering remission than those from White ethnic groups. There was a significant deprivation gradient with people living in the least deprived quintile of areas having an OR of entering remission of 1.13 (95% CI 1.09-1.18) compared to those in the most deprived areas.

People who were diagnosed with type 2 diabetes for less than two years had higher odds of entering remission (OR 2.78 (95% CI 2.68-2.88) for those diagnosed less than one year, and OR 1.12 (95% CI 1.08-1.17) for those diagnosed one to two years, compared to those diagnosed for 3 to 5 years). Baseline HbA1c of less than

48 mmol/mol (6.5%) was associated with greater odds of entering remission (OR 6.84 (95% CI 6.55-7.15) comparted to baseline HbA1c of 48 to 53 mmol/mol. Reduction in body mass index of 10% or more, and 5% to 9.9%, was associated with greater odds of entering remission (OR 3.57 (95% CI 3.42-3.72) and 1.78 (95% CI 1.71-1.85) respectively) compared to a reduction in body mass index of 0% to 4.9% (see Figure 2a).

Among the 208,260 people (9.1% of the cohort) in the early stages of type 2 diabetes (defined as diagnosed for less than two years, a baseline HbA1c less than 53 mmol/mol (7·0%) and prescribed metformin alone or no glucose lowering medications at baseline), with no history of heart failure, COPD, cancer, or dementia, higher odds of remission were associated with older age and living in less deprived areas. In this early-stage cohort, people from Asian and Black ethnic groups had lower odds of remission than White ethnic groups (Table 2). The multivariable adjusted odds of remission across BMI categories were greatest in people with a baseline body mass index of 20-24·9 kg/m^2 (OR 1·08 95% CI 1·01-1·15 compared to those with a baseline body mass index of 25-29·9 kg/m^2). Increasing baseline body mass index greater than 30 kg/m2 was associated with lower odds of entering remission (0·91 (95% CI 0·87-0·96) for 30-34·9 kg/m^2, 0·82 (95% CI 0·77-0·88) for 35-39·9 kg/m^2, 0·78 (95% CI 0·72-0·84) for 40 kg/m^2 or greater, compared to 25-29·9 kg/m^2). Compared to a 0-4·9% reduction in BMI, a reduction of 5-9·9% and 10% or greater was associated with ORs of entering remission of 1·89 (95% CI 1·77-2·02) and 3·54 (95% CI 3·28-3·82) respectively. Having a baseline HbA1c of less than 48mmol/mol (6·5%) versus 48-53 mmol/mol (6·5-7·0%) was associated with an OR of entering remission of 4·78 (95% CI 4·39-5·2) (see Figure 2b)..

Overall 3420 (8.9%) of the 38,530 of people who entered remission subsequently had a HbA1c measurement of 48mmol/mol (6.5%) or greater suggesting a return to hyperglycaemia in the diabetes range. Median time from entering remission of type 2 diabetes to this measurement was 190 days (IQR 144-247). 9175 (238 per 1000) people in remission had a HbA1c measurement that indicated that they continued to meet the definition of remission of type 2 diabetes (median follow up 294 days, IQR 222-361), and 25,940 (673 per 1000) people did not have any further HbA1c measurements within the study follow up period (median follow up time 148 days, IQR 77-235). When compared to those that stayed in remission, people who returned to diabetic hyperglycaemia had a lower mean reduction in BMI (-0.6% compared to -2.6% for those that stayed in remission, and -2.7% for those that did not have a further HbA1c measurement) and more likely to not be prescribed any glucose lowering medication at baseline (66.7% compared to 48.3% for those who stayed in remission and 46.3% for those that did not have a further HbA1c measurement). Of those meeting the criteria for remission, only 2110 (5·5%) had a diagnosis code for remission recorded in their electronic health record. There were no consistent differences in the characteristics of people with and without a diagnosis code for diabetes remission but there was considerable geographical variation in coding for remission by the 160 Clinical Commission Groups (health organisations with responsibility for commissioning healthcare for their local population) varying from 25% to less than 1%.

In sensitivity analysis, defining of remission based on only one HbA1c measurement less than 48 mmol/mol (6·5%) in the absence of a prescription for glucose lowering

medications in the preceding 90 days increased the number of people identified as in remission from 3420 (9.7 (95% CI 9.6-9.8) per 1000 person-years) to 91,405 (23·5 (95% CI 23·3-23·7) per 1000 person-years). The pattern of incidence rates by demographic and clinical characteristics were similar to the primary analysis (Table S3).

Discussion

In this nationally representative population-based study of over 2·2 million people with type 2 diabetes, the incidence of remission over a maximum of 21 months was low at about 1% per year overall and about 4·5% per year in those within the first year of diagnosis. However, there was also considerable variation in incidence by baseline and change in BMI, by ethnicity, and by duration of diagnosed diabetes. Amongst the sub-group of people who had been diagnosed for less than two years, with a baseline HbA1c of less than 53 mmol/mol (7·0%) and who also reduced their BMI by 10% or more who formed 5.2% of the cohort the incidence of remission rose to 8% per year. This implies that the opportunity to achieve remission is greatest in the period immediately after diagnosis, particularly in the context of intensive lifestyle interventions.[3]

Greater remission rates were consistently associated with weight loss and degree of weight loss. The higher incidence of remission in people with a very low baseline BMI may reflect underlying co-morbidities and consequent unintentional weight loss. Bariatric surgery was associated with very high incidence of entering remission (169·5 (95% CI 152·7-187·7) per 1000 person years). However, the absolute number of people with a record of undergoing bariatric surgery in the NHS during the

study period was small (1390 or 0·06%) and the characteristics and motivations of these people may have differed which increases the likelihood of achieving remission.

Not being prescribed any glucose lowering medications in the baseline period was associated with an incidence of remission approximately five times higher than in those prescribed metformin as their only glucose lowering medication whilst remission was rare in those who were prescribed non-insulin, non-metformin glucose lowering medications, or insulin, in the baseline period. These findings are likely to reflect difficulty in controlling hyperglycaemia rather than any remission inhibiting effect of the medications, or that people on more than one drug will have more advanced diabetes. Those living in the least deprived areas and those from White ethnic groups were more likely to enter remission than people in the respective comparison groups, This may be explained by people from non-White ethnic groups having higher HbA1c at diagnosis and poorer HbA1c trajectories following diagnosis of type 2 diabetes[17, 18]. Our findings are in contrast to a US study where higher adjusted incidence of remission occurred in those from Black ethnic groups[19]. Further exploration of physical, psychological, social and healthcare factors which may affect awareness, motivation and capacity for entering remission amongst people of varying ethnic backgrounds in England is warranted.

We found men to have slightly lower odds of remission overall, perhaps due to their generally higher levels of HbA1c. However, this finding was reversed and not significant in the sub-set with fewer than two years since diagnosis, and warrants further investigation. People in older age groups had a higher incidence of remission

of type 2 diabetes than those in younger age groups which could be attributable to lower average body mass index (it is well known average BMI at diabetes diagnosis is lower in older people and therefore the weight loss needed to move into remission is less[20]). Also, older people may have a higher prevalence of co-morbidities that may be associated with unintentional weight loss. Policies focusing on lifestyle interventions to increase rates of remission of type 2 diabetes should be aware of these inequalities and incorporate measures that aim to address them.

Only 5·5% of people meeting the criteria for remission had a diagnosis code related to remission of diabetes. Given that some definitions of remission of type 2 diabetes require a longer period of glycaemia below the diabetic range than used in this analysis, the low proportion of coded remissions may be due to the relatively short follow up period. However, it may also reflect a lack of awareness of the concept of remission of diabetes, with clinicians having traditionally considered type 2 diabetes to be a chronic, progressive disease. Additionally, it may simply be lack of awareness of such codes. There may also be concerns about the impact of these codes on routine diabetes monitoring and screening for complications, incentive payments or on-going care arrangements. Interventions are needed to raise awareness and encourage the appropriate use of these codes, particularly as intensive lifestyle interventions, new weight loss medications, and bariatric surgery are more widely deployed. However, in the meantime, our findings suggest that codes for remission should not be relied upon for research purposes.

Intensive lifestyle intervention studies in the UK show that approximately a third of selected trial participants undergoing very low calorie diet and large weight loss

enter, and remain in, remission of type 2 diabetes over a period of two to five years.[3,4,21] The Look AHEAD study showed an incidence of remission of type 2 diabetes of 11.5% at one year and 7.3% at four years in the intensive lifestyle intervention group and 2.0% at both one and four years in the group who received three group sessions per year.[5] These rates are higher than found in this analysis but are likely to reflect the impact of intensive interventions in selective trial populations. However, this study sought to assess the incidence of remission in a real-world community setting where evidence is more sparse and incidence is considerably lower. Whilst this cohort may have included a small number of people enrolled in specific trials focusing on remission, the majority will not have received the intensive support that goes alongside specific research studies. The overall incidence of remission found is similar to a community based study in the United States which found a 7 year cumulative incidence of remission of 1·6% rising to 4·6% in those whose diabetes was diagnosed less than two years previously.[22]

In 2020 the NHS in England established a low-calorie diet pilot programme to test the effectiveness of intensive lifestyle interventions within live NHS environments for people within six years of diagnosis with type 2 diabetes.[23] The results from this current study can be used as a baseline for monitoring the incidence and characteristics of remission following the possible roll-out of this programme in England, and suggest that codes for remission of diabetes are currently of limited value.

For this analysis, remission was defined as two consecutive HbA1c measurements at least 26 weeks apart which were less than 48 mmol/mol (6·5%) with no

prescription for glucose lowering medication between these measurements and at least 90 days prior to each HbA1c measurement. The recent consensus statement on the definition and interpretation of remission in type 2 diabetes sets out definitions of remission of type 2 diabetes depending on the route by which remission is achieved (pharmacotherapy, bariatric surgery or lifestyle interventions).[10] In each case, remission is defined as a HbA1c measurement less than 48 mmol/mol (6.5%) at least three months after the cessation of glucose lowering medications and at least three months after bariatric surgery or six months after the start of lifestyle interventions. However, routinely collated data records the date prescriptions are issued and it is difficult to ascertain the exact date at which the individual ceased to take the prescribed medications and our dataset (like most routine healthcare records) did not include data on lifestyle interventions. These factors mean that there are some differences between the definition in the consensus statement and the criteria used to identify remission in this study.

In this analysis, follow-up was limited to a maximum period of 21 months during which 8·9% of people meeting the criteria for remission went on to have a HbA1c measurement indicating a return to diabetic hyperglycaemia. Those people who returned to hyperglycaemia in the diabetic range during the follow up period of this study had a smaller mean reduction in body mass index and were more likely to not be prescribed glucose lowering medication at baseline than those that remained in remission or did not have subsequent HbA1c measurements. This highlights the potentially transient nature of remission in the context of routine traditional care and emphasises the need for longer term follow up of these individuals.

The strength of this study lies in the large population-based cohort which includes people registered at 98·2% of general practices in England including nearly 2.3 million people with type 2 diabetes. By combining data on routinely recorded HbA1c measurements and prescriptions for glucose lowering medications, it provides a reliable assessment of the incidence of remission of type 2 diabetes using the specified definition in people receiving routine current care. The relatively short follow up time is a weakness limiting inferences about the durability of remission but follow up was limited to 31st December 2019 to avoid altered patterns of behaviour and healthcare provision due to the COVID-19 pandemic. Data on prescriptions for glucose lowering medications were collected for the first time in the 2017/18 data collection and therefore earlier datasets could not be used. The NDA does not yet collate data on lifestyle interventions therefore it is not currently possible to identify the means through which individuals achieved remission, although planned linkage with national datasets relating to lifestyle interventions should permit this in future years. However, we include data on remission from bariatric surgery due to linkage of our data with hospital data.

It is possible that some people entered remission of type 2 diabetes following unintentional weight loss due to ill health meaning that their remission may not represent a positive health change. We have tried to compensate for this limitation by using hospital discharge data to identify people with co-morbidities that are associated with unintentional weight loss, but we recognise it is difficult to differentiate intentional versus unintentional weight loss. People who received bariatric surgery outside the National Health Service will not have had their

procedures recorded and so the numbers of such operations will have been under-estimated.

This study has identified that remission of type 2 diabetes does occur within a community setting among a population receiving standard clinical care, but the absolute incidence is low. The characteristics of those who did go into remission will help the design of lifestyle intervention programmes for induction and maintenance of remission. Longer term follow-up of this cohort of people entering remission to identify their glycaemic trajectories and the subsequent risk of macro- and micro vascular disease as recommended by the recent consensus statement on the definition and interpretation of remission in type 2 diabetes[10] would be informative.

Acknowledgements

The authors thank Liz Coyle, University of Glasgow, for her assistance in the preparation of this article.

Funding

NH is funded by Diabetes UK and NHS England and NHS Improvement. KK is supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM) and the NIHR Leicester Biomedical Research Centre (BRC). NS is supported by the British Heart Foundation Research Excellence Award (RE/18/6/34217).

Author contributions

The study was designed by NS, KK, BY, EWG, SHW and NH. NH undertook the statistical analysis. All authors reviewed the methods, assisted in writing the paper and reviewed the final manuscript. NH is the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Declaration of interests

KK, BY and JV are members of the NDA Research Advisory Group. KK has acted as a consultant, speaker, or received grants for investigator-initiated studies for Astra Zeneca, Novartis, Novo Nordisk, Sanofi-Aventis, Lilly, and Merck Sharp & Dohme, Boehringer Ingelheim, Bayer, Berlin-Chemie AG / Menarini Group, Janssen, and Napp. JV is National Clinical Director for Diabetes and Obesity at NHS England & NHS Improvement. NS has received grant from AstraZeneca, Boehringer Ingelheim, and Roche Diagnostics, and personal fees from Afimmune, Amgen, AstraZeneca, Eli Lilly, Hanmi Pharmaceuticals, Merck Sharp & Dohme, Novartis, Novo Nordisk, Pfizer, and Sanofi outside the submitted work. All other authors declare no relationships or activities that could appear to have influenced the submitted work.

References

1 Public Health England. Diabetes Prevalence Model 2016. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/612306/Diabetesprevalencemodelbriefing.pdf (accessed Aug 17, 2021).

2 International Diabetes Federation. IDF Diabetes Atlas 9th edition 2019. https://diabetesatlas.org/en/ (accessed May 27, 2021).

3 Lean ME, Leslie WS, Barnes AC, *et al.* Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet (London, England)* 2018; **391**: 541–51.

4 Lean MEJ, Leslie WS, Barnes AC, *et al.* Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019; **7**: 344–55.

5 Gregg EW, Chen H, Wagenknecht LE, *et al.* Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA - J Am Med Assoc* 2012; **308**: 2489–96.

6 Cummings DE, Arterburn DE, Westbrook EO, *et al.* Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomised controlled trial. *Diabetologia* 2016; **59**: 945–53.

7 Sjöström L, Peltonen M, Jacobson P, *et al.* Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA - J Am Med Assoc* 2014; **311**: 2297–304.

8 Mingrone G, Panunzi S, De Gaetano A, *et al.* Bariatric Surgery versus Conventional Medical Therapy for Type 2 Diabetes. *N Engl J Med* 2012; **366**: 1577–85.

9 Cummings DE, Cohen R V. Bariatric/Metabolic Surgery to Treat Type 2 Diabetes in Patients With a BMI <35 kg/m 2. *Diabetes Care* 2016; **39**: 924–33.

10 Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK et al Consensus Report: Definition and Interpretation of Remission in Type 2 Diabetes *Diabetes Care* 2021; **44** (10): 2438-2444

11 Holman N, Knighton P, Wild SH, *et al.* Cohort profile: National Diabetes Audit for England and Wales. *Diabet Med* 2021; : e14616.

12 National Diabetes Audit - Report 1 Care Processes and Treatment Targets 2017-18, Full Report - NHS Digital. https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit/report-1-care-processes-and-treatment-targets-2017-18-full-report (accessed July 12, 2021).

13 De Lusignan S, Sadek N, Mulnier H, Tahir A, Russell-Jones D, Khunti K Miscoding, misclassification and misdiagnosis of diabetes in primary care *Diab Med* 2012; **29** (2): 181-9

14 Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the Primary Care Diabetes Society (PCDS). *Br J Diabetes* 2019; **19**: 73–6.

15 English Indices of Deprivation 2019. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019 (accessed April 22, 2021).

16 Breslow NE, Day NE. Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. *IARC Sci Publ* 1987; : 1–406.

17 https://onlinelibrary.wiley.com/doi/epdf/10.1002/dmrr.3015

18 Independent Effect of Ethnicity on Glycemia in South Asians and White Europeans | Diabetes Care | American Diabetes Association (diabetesjournals.org)

19 Incidence of remission in adults with type 2 diabetes: the diabetes & aging study - PubMed (nih.gov)

20 https://pubmed.ncbi.nlm.nih.gov/32435821/

21 Dambha-Miller H, Day AJ, Strelitz J, Irving G, Griffin SJ. Behaviour change, weight loss and remission of Type 2 diabetes: a community-based prospective cohort study. *Diabet Med* 2020; **37**: 681–8.

22 Karter AJ, Nundy S, Parker MM, Moffet HH, Huang ES. Incidence of Remission in Adults With Type 2 Diabetes: The Diabetes & Aging Study. *Diabetes Care* 2014; **37**: 3188–95

23 NHS England » Low calorie diets to treat obesity and Type 2 diabetes. 2021. https://www.england.nhs.uk/diabetes/treatment-care/low-calorie-diets/ (accessed July 8, 2021)

22

Tables and Figures

Table 1: Characteristics of people who were alive on 1st April 2018 who did not and did achieve remission (see text for definition) of diagnosed type 2 diabetes before 31st December 2019

	Not in remission		In remission					
			All in remission		Without co-morbidity*		With co-morbidity+	
	n	%	n	%	n	%	n	%
Persons	2,259,170		38,530		30,465		8,065	
Females	980,380	43·4%	18,620	48·3%	14,795	48·6%	3,825	47·4%
Males	1,278,795	56·6%	19,910	51·7%	15,670	51·4%	4,240	52·6%
Age (years)								
<40	65,555	2·9%	1,270	3·3%	1,240	4·1%	25	0·3%
40-49	200,890	8·9%	2,790	7·2%	2,700	8·9%	95	1·2%
50-59	452,150	20·0%	5,810	15·1%	5,350	17·6%	460	5·7%
60-69	598,680	26·5%	8,895	23·1%	7,500	24·6%	1,395	17·3%
70-79	585,785	25·9%	11,070	28·7%	8,085	26·5%	2,980	36·9%
≥80	356,110	15·8%	8,695	22·6%	5,590	18·3%	3,110	38·6%
Mean (SD)	66·2 (13·1)		68·6 (13·8)		66·6 (14)		76·1 (10·2)	
Quintiles of deprivation index								
Most deprived	554,495	24·5%	8,075	21·0%	6,260	20·5%	1,810	22·4%
2nd most deprived	504,825	22·3%	8,185	21·2%	6,450	21·2%	1,735	21·5%
3rd most deprived	460,745	20·4%	8,155	21·2%	6,450	21·2%	1,705	21·1%
2nd least deprived	406,645	18·0%	7,595	19·7%	6,040	19·8%	1,550	19·2%
Least deprived	331,810	14·7%	6,510	16·9%	5,255	17·2%	1,260	15·6%
Missing	650	0·03%	10	0·03%	5	0·02%	5	0·06%
Ethnicity								
Asian	261,060	11·6%	2,785	7·2%	2,465	8·1%	295	3·7%
Black	108,385	4·8%	1,535	4·0%	1,325	4·3%	200	2·5%
Mixed	23,345	1·0%	330	0·9%	285	0·9%	45	0·6%
White	1,511,220	66·9%	27,990	72·6%	21,320	70·0%	6,490	80·5%
Other	107,060	4·7%	1,220	3·2%	1,090	3·6%	120	1·5%
Missing	247,855	11·0%	4,920	12·8%	3,980	13·1%	915	11·3%
Duration (years)								
<1	141,620	6·3%	11,690	30·3%	9,910	32·5%	1,780	22·1%
1-2	267,195	11·8%	7,050	18·3%	5,765	18·9%	1,285	15·9%
3-5	255,040	11·3%	4,740	12·3%	3,770	12·4%	970	12·0%
5-9	608,535	26·9%	8,125	21·1%	6,215	20·4%	1,910	23·7%
10-14	507,925	22·5%	4,530	11·8%	3,210	10·5%	1,320	16·4%
≥15	478,505	21·2%	2,385	6·2%	1,590	5·2%	795	9·9%
Mean (SD)	9·9 (7·6)		5·1 (5·9)		4·8 (5·7)		6·6 (6·6)	
HbA1c (mmol/mol)								
Mean (SD) in 2017/18	57·3 (15·1)		45·9 (8·1)		46 (8·2)		45·5 (7·6)	
Mean change (SD)	0·2 (11·8)		-4·1 (7·8)		-4·2 (7·9)		-3·8 (7·4)	
BMI (kg/m^2)								
Mean (SD) in 2017/18	31 (6·5)		30·6 (6·6)		30·9 (6·5)		29·5 (6·5)	
Change in BMI (%)								
≥10% reduction	106,315	4·7%	3,870	10·0%	3,590	11·8%	875	10·8%
5-9·9% reduction	220,725	9·8%	4,130	10·7%	3,930	12·9%	755	9·4%
0-4·9% reduction	639,835	28·3%	6,935	18·0%	6,635	21·8%	1,235	15·3%
0·1-4·9% increase	479,820	21·2%	4,575	11·9%	4,320	14·2%	865	10·7%
≥5% increase	179,805	8·0%	2,125	5·5%	1,965	6·5%	455	5·6%
Missing	632,675	28·0%	16,895	43·8%	15,975	52·4%	3,880	48·1%
Mean (SD) change 2017/18 to 2018/19	-0·2% (8·1%)		-2·5% (10·2%)		-2·5% (10%)		-2·2% (11%)	
Co-morbidities								

Heart failure	143,105	6·3%	2,585	6·7%	-	-	2,585	32·1%
Cancer	162,090	7·2%	3,180	8·3%	-	-	3,180	39·4%
COPD	150,135	6·6%	3,115	8·1%	-	-	3,115	38·6%
Dementia	59,135	2·6%	1,220	3·2%	-	-	1,220	15·1%
Any comorbidity	408,440	18·1%	8,065	20·9%	-	-	8,065	100·0%
Bariatric surgery	1,020	0·05%	370	0·96%	315	1·03%	55	0·7%
Treatment in 2017/18								
None	179,250	7·9%	18,735	48·6%	15,060	49·4%	3,675	45·6%
Metformin only	816,900	36·2%	15,675	40·7%	12,430	40·8%	3,240	40·2%
Other non-insulin glucose lowering agents +/- metformin	1,164,340	51·5%	3,850	10·0%	2,750	9·0%	1,100	13·6%
Insulin +/- other glucose lowering agents	98,680	4·4%	270	0·7%	220	0·7%	50	0·6%

* - no history of a hospital admission for heart failure, cancer, chronic obstructive pulmonary disease or dementia between 1st April 2015 and 31st March 2019

+ - history of a hospital admission for heart failure, cancer, chronic obstructive pulmonary disease or dementia between 1st April 2015 and 31st March 2019

Figure 1: Incidence of remission of type 2 diabetes per 1000 person years

Figure 2a: Forest plot of odds ratios from multivariable model including all factors for demographic and clinical characteristics associated with remission of type 2 diabetes in whole cohort

Figure 2b: Forest plot of odds ratios from multivariable model including all factors for demographic and clinical characteristics associated with remission of type 2 diabetes in people with early stage Type 2 diabetes (a baseline HbA1c <53 mmol/mol, duration of diagnosed diabetes of two year or less and prescribed only metformin or no glucose lowering medication at baseline)

Table 2: Characteristics of people who entered remission by remission status at the end of follow up

	Stayed in remission		Returned to diabetic hyperglycaemia		No follow up HbA1c	
	n	%	n	%	n	%
Number	9,175		3,420		25,935	
Sex						
Female	4,460	48.6%	1,600	46.8%	12,560	48.4%
Male	4,715	51.4%	1,815	53.1%	13,380	51.6%
Age						
<40 years	265	2.9%	80	2.3%	925	3.6%
40-49 years	635	6.9%	225	6.6%	1,935	7.5%
50-59 years	1,390	15.1%	505	14.8%	3,915	15.1%
60-69 years	2,225	24.3%	815	23.8%	5,850	22.6%
70-79 years	2,700	29.4%	1,095	32.0%	7,275	28.1%
80+ years	1,960	21.4%	700	20.5%	6,035	23.3%
Mean (SD)	68.5 (13.4)		68.9 (12.9)		68.6 (14.1)	
Deprivation						
Most deprived	1,935	21.1%	635	18.6%	5,505	21.2%
2nd most deprived	1,935	21.1%	660	19.3%	5,590	21.6%
3rd most deprived	1,970	21.5%	780	22.8%	5,405	20.8%
2nd least deprived	1,805	19.7%	740	21.6%	5,050	19.5%
Least deprived	1,530	16.7%	600	17.5%	4,380	16.9%
Missing	-	0.00%	-	0.00%	10	0.04%
Ethnicity						
Asian	600	6.5%	280	8.2%	1,880	7.2%
Black	345	3.8%	115	3.4%	1,065	4.1%
Mixed	65	0.7%	25	0.7%	235	0.9%
White	6,795	74.1%	2,435	71.2%	18,585	71.7%
Other	255	2.8%	100	2.9%	855	3.3%
Missing	1,110	12.1%	470	13.7%	3,315	12.8%
Duration						
<1 year	3,125	34.1%	1,300	38.0%	7,265	28.0%
1-2 years	1,645	17.9%	620	18.1%	4,785	18.4%
3-5 years	1,065	11.6%	410	12.0%	3,270	12.6%
5-9 years	1,845	20.1%	600	17.5%	5,680	21.9%
10-14 years	980	10.7%	315	9.2%	3,235	12.5%
15+ years	515	5.6%	180	5.3%	1,690	6.5%
Mean (SD)	4.8 (5.8)		4.3 (5.2)		5.4 (6.1)	
HbA1c (mmol/mol) in 2017/18						
<48	4,250	46.3%	930	27.2%	11,695	45.1%
48-53	4,360	47.5%	2,225	65.1%	12,215	47.1%
54-58	335	3.7%	185	5.4%	1,200	4.6%
59-74	165	1.8%	65	1.9%	580	2.2%
75-85	35	0.4%	5	0.1%	105	0.4%
86+	25	0.3%	10	0.3%	140	0.5%
Mean (SD)	45.3 (7.6)		47.8 (6)		45.9 (8.4)	
Mean (SD) change 17/18 to 18/19	-4.1 (7.4)		-4.1 (6)		-4.1 (8.1)	
BMI (kg/m^2) in 2017/18						
<20	140	1.5%	50	1.5%	445	1.7%
20-24.9	1,260	13.7%	445	13.0%	3,490	13.5%
25-29.9	2,690	29.3%	1,070	31.3%	7,140	27.5%
30-34.9	2,180	23.8%	850	24.9%	5,795	22.3%
35-39.9	940	10.2%	350	10.2%	2,660	10.3%
40+	640	7.0%	190	5.6%	1,850	7.1%
Missing	1,325	14.4%	465	13.6%	4,555	17.6%
Mean (SD)	30.5 (6.5)		30.3 (6)		30.6 (6.7)	
Change in BMI (%)						
≥10% reduction	970	10.6%	140	4.1%	2,760	10.6%
5-9.9% reduction	945	10.3%	345	10.1%	2,840	11.0%
0-4.9% reduction	1,695	18.5%	780	22.8%	4,460	17.2%

0.1-4.9% increase	1,080	11.8%	500	14.6%	2,995	11.5%
≥5% increase	475	5.2%	190	5.6%	1,460	5.6%
Missing	4,010	43.7%	1,460	42.7%	11,425	44.1%
Mean (SD) change 17/18 to 18/19	-2.6% (9.9%)		-0.6% (9.6%)		-2.7% (10.4%)	
Co-morbidities						
Heart failure	570	6.2%	215	6.3%	1,800	6.9%
Cancer	735	8.0%	280	8.2%	2,165	8.3%
COPD	725	7.9%	265	7.7%	2,125	8.2%
Dementia	215	2.3%	70	2.0%	935	3.6%
Any comorbidity	1,830	19.9%	685	20.0%	5,545	21.4%
Bariatric surgery	135	1.47%	10	0.29%	225	0.87%
Treatment in 2017/18						
None	4,435	48.3%	2,280	66.7%	12,020	46.3%
Metformin only	3,790	41.3%	890	26.0%	10,990	42.4%
Other non-insulin glucose lowering	875	9.5%	230	6.7%	2,750	10.6%
Insulin +/- other glucose lowering	75	0.8%	20	0.6%	180	0.7%