

Incident type 2 diabetes in a population with impaired glucose regulation and the effect of early regression to normoglycaemia.

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Novelty statement:

- We provide contemporary estimates of the natural history of impaired glucose regulation, which are vital for service planning.

- Reductions in weight and waist circumference were associated with regression to normal glucose tolerance, which was in turn associated with a much lower subsequent risk of type 2 diabetes.
- These data are from a population-based UK cohort and so are more generalisable than existing data from randomised controlled trials.
- A message for those identified with intermediate hyperglycaemia could be that if they lose any weight in the year after diagnosis then they may be almost twice as likely to achieve normal glucose tolerance.

ABSTRACT

Aims. To report contemporary regression rates from impaired glucose regulation to normal glucose tolerance, identify modifiable factors associated with early regression, and establish whether it affects subsequent diabetes risk in a population-based cohort.

Methods. Participants with impaired glucose regulation (impaired fasting glucose and/or impaired glucose tolerance on a 75g-OGTT) at baseline in UK-based ADDITION-Leicester had annual type 2 diabetes re-screens for five years or until diabetes diagnosis. Logistic regression models investigated modifiable risk factors for regression to normal glucose tolerance at one year (n=817). Cox regression models estimated subsequent diabetes risk (n=630).

Results. At one year, 54% of participants had regressed to normal glucose tolerance, and 6% had progressed to diabetes. Regression to normal glucose tolerance was associated with weight loss of 0.1-3% (adjusted OR [95% CI]: 1.81 [1.08, 3.03] compared with maintaining or gaining weight) and waist circumference reduction of >3cm (1.78 [1.03, 3.06] compared with maintaining or increasing waist circumference). Those with normal glucose tolerance at one year subsequently had lower diabetes risk than those who remained with impaired glucose regulation (adjusted HR 0.19 [95% CI 0.10, 0.37]).

Conclusions. Early regression to normal glucose tolerance was associated with reduced diabetes incidence, and might be induced by small reductions in weight or waist circumference. If confirmed in experimental research, this could be a clear and achievable target for individuals diagnosed with impaired glucose regulation.

INTRODUCTION

Impaired glucose regulation (IGR; also known as 'prediabetes' or 'intermediate hyperglycaemia') increases risk of type 2 diabetes mellitus (T2DM), can be identified using fasting glucose, two-hour glucose or HbA1c, and has become increasingly prevalent over the last two decades. For example, in the United States, it is estimated that the prevalence of IGR (defined in that study as HbA1c between 39mmol/mol [5.7%] to 46mmol/mol [6.4%]) more than doubled from 5.8% in 1988-1994 to 12.4% in 2005-2010 [1]. In the United Kingdom, a recent study found that approximately one in three adults have IGR (defined by the same HbA1c criteria) from which more than one million incident T2DM cases are predicted annually [2]. Appropriately-targeted, effective primary prevention strategies are therefore needed. Randomised controlled trials have demonstrated that dietary change, physical activity and pharmacotherapy can delay or prevent progression from IGR [3-5]. Real-world replication of these results is challenging, with 'pragmatic' programmes of lifestyle interventions typically achieving 2-3% weight loss after one year, compared with 9-10% in randomised controlled trials [6]. Identifying individuals achieving early normal glucose tolerance (NGT) may improve the efficiency of prevention programmes by allowing them to concentrate on those at greatest T2DM risk.

Approximately half of those with IGR may revert to NGT due to measurement variability or lifestyle change following identification [7, 8], but this conclusion is based on studies that are at least 20 years old, or concentrated on progression to diabetes, rather than regression to NGT [9-14]. It is unclear whether regression rates have changed over time, or whether regression to NGT is associated with lower diabetes risk outside of the Diabetes Prevention Programme, which included a highly structured intervention [15, 16]. Furthermore, we were

interested in identifying modifiable factors for regression to NGT, because many healthcare organisations now routinely screen for IGR resulting in an incredibly high number of IGR diagnoses, thus public health approaches for preventing T2DM in these people are urgently needed.

We aimed to report regression rates from IGR to NGT, establish whether early regression affects cumulative diabetes incidence, and identify modifiable factors associated with achieving regression using a well-characterised, non-intervention cohort in a clinically relevant, contemporary population.

PATIENTS AND METHODS

Definitions of NGT, IGR and T2DM (WHO 1999)

NGT and IGR were diagnosed using 75g-OGTT. T2DM was diagnosed using 75g-OGTT or by the participant's own physician. NGT was defined as fasting glucose $<6.1\text{mmol/l}$ and 2-hour glucose $<7.8\text{mmol/l}$, IGR as impaired fasting glucose (IFG; fasting glucose $6.1\text{--}6.9\text{mmol/l}$) and/or impaired glucose tolerance (IGT; 2-hour glucose $7.8\text{--}11.0\text{mmol/l}$), and T2DM as fasting glucose $\geq 7.0\text{mmol/l}$ and/or 2-hour glucose $\geq 11.1\text{mmol/l}$.

Study Population

The ADDITION-Prediabetes Cohort Study is an observational follow-up of participants with IGR at baseline in ADDITION-Leicester (NCT00318032), which is described in detail elsewhere [17, 18]. Briefly, people from 20 representative general practices in Leicester,

Leicestershire and Rutland, UK were invited for diabetes screening if they were aged 40-75 years (25-75 years for South Asians) inclusive. Exclusion criteria were pre-existing diabetes, terminal illness, or pregnancy. Participants were screened with a 75g oral glucose tolerance test (75g-OGTT) and WHO 1999 diagnostic criteria applied [19]. Participants with IFG and/or IGT at baseline (2004-2007) were invited to join the ADDITION-Prediabetes cohort (2005-2013). They received rudimentary lifestyle advice consistent with standard practice at the time, and were invited to annual re-screens identical to the baseline assessment for a total of five visits. If diabetes was diagnosed during a follow-up visit, a second 75g-OGTT was performed within a week and if the T2DM diagnosis was confirmed then the participant was referred to their own physician and they exited the study. If the second test was not in the diabetes range, the participant continued in the study. A physician diagnosis of diabetes at any time during follow-up was also considered an endpoint. If, at follow-up, the participant was diagnosed with NGT or IGR (IFG and/or IGT) they continued in the study. The study received ethical approval from University Hospitals of Leicester (UHL09320) and Leicestershire Primary Care Research Alliance (64/2004) local research ethics committees and was conducted in accordance with the Helsinki Declaration. All participants gave written informed consent.

Variables

At each visit, participants provided information on demographics, smoking status, alcohol consumption, previous medical history and family history of disease. HbA_{1c} and anthropometric measurements were recorded by trained staff following standard operating procedures. Height was measured to the nearest 0.1cm using a rigid stadiometer and weight

in light indoor clothing to the nearest 0.1kg with a Tanita scale (Tanita, Europe). Body mass index (BMI; kg/m^2) was categorised as normal ($<25\text{kg/m}^2$), overweight ($25.0\text{--}29.9\text{kg/m}^2$) or obese ($\geq 30\text{kg/m}^2$). Waist circumference was measured at the mid-point between the lower costal margin and the level of the anterior superior iliac crest to the nearest 0.1cm. Socio-economic status was measured using Index of Multiple Deprivation scores, which are a postcode-based measure of socio-economic status; higher scores indicate higher deprivation. Physical activity was self-reported using a validated 7-day questionnaire (IPAQ) [20]. Total METS (metabolic equivalents) per week were estimated by summing the walking, moderate and vigorous METS.

Statistical analysis

Baseline characteristics were summarised as mean (standard deviation) for continuous variables and count (percentage) for categorical variables for the whole cohort, and by glycaemic status at one year with comparisons by ANOVAs and chi-squared tests, respectively. Logistic regression estimated the association between changes in modifiable factors from baseline to one year and regression to NGT at one year with adjustment for age (years, continuous), sex (men, women), ethnicity (White, non-White), social deprivation score (continuous), baseline glucose status (IFG, IGT, both), BMI (kg/m^2 , continuous), family history of diabetes (yes, no), and physical activity (total METS/week, continuous). A Kaplan-Meier graph and Cox survival models estimated the HR (95% CI) for incident T2DM in those who regressed to NGT at one year compared with those who did not. Person-time was included from one year to T2DM diagnosis, loss to follow-up, or end of follow-up, whichever was earliest. Those not diagnosed with T2DM were censored at their last follow-up. Four

Cox models were fitted: 1) Unadjusted, 2) Adjusted for age, sex, ethnicity and social deprivation score, 3) Additionally adjusted for baseline glucose status, and 4) Additionally adjusted for BMI, family history of diabetes, physical activity, and weight change from baseline to one year (kg, continuous). As sensitivity analyses, the Cox models were re-fitted with T2DM diagnosis by 75g-OGTT, physician diagnosis, and/or HbA_{1c} ≥ 48 mmol/mol (6.5%) to account for changes in T2DM diagnostic criteria introduced after the study started [21]. In these analyses, participants were defined as having developed T2DM if they met at least one of the diagnostic criteria for T2DM (i.e. were diagnosed with T2DM by at least one of 75g-OGTT, physician diagnosis, or HbA_{1c}). Participants with HbA_{1c} ≥ 48 mmol/mol (6.5%) at baseline were excluded from sensitivity analyses. Analyses were performed in Stata v14. All p-values are two-sided. Missing data were not imputed.

RESULTS

Participants

Of the 6749 participants screened in ADDITION-Leicester, 1080 had IGR and were invited to join the ADDITION-Prediabetes cohort (Fig. 1); 910 (84.3%) joined. The age ($p=0.422$) and ethnicity ($p=0.287$) distribution were similar among those who did and did not join, but women were more likely to join than men ($p=0.038$). Participants were excluded because they did not attend the first follow-up (91; 10.0%) or their glycaemic status at one year was unknown (2; 0.2%). Therefore, 817 (89.8%) participants were analysed (mean [range] time to one year follow-up = 1.2 [0.5-1.5] years). Mean (SD) age was 60 (10) years (Table 1). There were approximately equal numbers of men (47%) and women (53%), a quarter of

participants were non-White, and only 14% were in the normal BMI category. At baseline, 18% of participants had IFG, 68% had IGT, and 14% had both IFG and IGT.

Regression to NGT at one year

At one year, 441 (54.0%) had regressed to NGT, 329 (40.3%) still had IGR, and 47 (5.8%) had developed T2DM (42 diagnosed at study visit; 5 by their own physician). Those who regressed to NGT were slightly younger at baseline than those who did not ($p=0.07$; Table 1), had lower fasting glucose ($p<0.001$), 2-hour glucose ($p<0.001$), HbA_{1c} ($p<0.001$), waist circumference ($p<0.001$), and weight ($p<0.01$) at baseline on average, and were less likely to be obese ($p<0.01$). Among those who did not regress to NGT, 22% had both IFG and IGT compared with only 7% of those who did regress ($p<0.001$).

After adjustment, participants who had lost 0.1-3% (3% was the median weight loss among those who lost weight) of their baseline weight by one year (18.6%) were significantly more likely to regress to NGT than those who maintained their baseline weight or gained weight (adjusted OR 1.81; 95% CI 1.08, 3.03; Table 2). Those who lost >3% of their baseline weight were also more likely to regress to NGT compared with those who maintained or gained weight, but this was not significant (adjusted OR 1.30; 95% CI 0.81, 2.09). There was also a non-significant benefit in losing 0.1-3cm (the median observed reduction among those in whom waist circumference decreased) of baseline waist circumference (adjusted OR 1.15; 95% CI 0.65, 2.02) and a greater, significant benefit in losing >3cm of baseline waist circumference (adjusted OR 1.78; 95% CI 1.03, 3.06). Regressing to NGT was not significantly associated with change in physical activity, alcohol consumption, or statin treatment

($p > 0.05$ for all). There were too few smokers at baseline ($n=58$) to allow a meaningful analysis of smoking cessation, and diet was not measured.

Further follow-up after one year

The 770 participants without diabetes at one year remained eligible for annual re-screening; 630 (81.1%) attended at least one additional follow-up visit, and were included in the remaining analyses. There were no significant differences between the baseline characteristics of those who did ($n=630$) and did not ($n=140$) return for further follow-up, except that women with IGR at one year were more likely to withdraw than men, and people with NGT at one year who withdrew had a higher baseline weight than those who did not (Supplementary Table 1).

After the one year follow-up, the mean (range) of the further follow-up was 2.8 (0.0-4.4) years. A median of three further follow-up visits were attended (i.e. four follow-up visits in total). During this time, 81 incident T2DM cases were diagnosed (72 at a study visit; 9 by their own physician) over 1752 person-years (incidence rate = 46.3 [95% CI 37.3, 57.6] per 1000 person-years).

People with NGT at one year were more likely to subsequently remain diabetes-free than those with IGR at one year (Fig. 2). This reflects the T2DM incidence rates of 90.0 (95% CI 70.0, 115.7) and 18.7 (95% CI 12.1, 29.0) per 1000 person-years for those who did not and did regress to NGT at one year, respectively. The unadjusted HR for T2DM was 0.20 (95% CI 0.12, 0.33) for regression to NGT compared with not regressing, which was largely unchanged in adjusted models (Table 3). In sensitivity analyses that included HbA_{1c} in T2DM

diagnosis, the association between regression to NGT and future T2DM risk was attenuated, but regression still had a strong, highly significant protective effect (Supplementary Table 2).

DISCUSSION

In this contemporary population, 54% of those with IGR regressed to NGT at one year without a highly structured, formal intervention. This is comparable with historical cohorts suggesting that the natural history of IGR has remained fairly stable over time [7-14]. Notably, the percentage of participants with both IFG and IGT at baseline was much higher among those who did not regress at one year compared with those who did regress. This confirms previous findings indicative of an incremental relationship between glucose concentration and diabetes risk below the T2DM diagnostic threshold. This implies that classifications encapsulating IFG and IGT have a greater degree of beta cell dysfunction and more advanced pathophysiology. The individuals who regressed from IGR to NGT within one year developed 71 fewer T2DM cases per 1000 person-years in subsequent follow-up than those who did not regress. Our estimated progression rate from IGR to T2DM of 46 cases per 1000 person-years is in line with previous studies [22].

To our knowledge, we are the first to investigate changes that an individual with IGR can make to improve their chance of regressing to NGT. In addition to regression being associated with reduced diabetes incidence, dysglycaemia is associated with adverse outcomes even below the diabetes thresholds [23] providing further motivation for attempting to regress to NGT, rather than remaining in an IGR state.

The most important factor appeared to be decreases in body size, with higher regression rates among those who lost any weight in the year following diagnosis compared with those who did not, although we found no evidence of a dose-response relationship. Weight loss of 0.1-3% and waist circumference decrease of ≥ 3 cm were associated with ORs of almost two, which are similar to or greater than the pooled ORs of regression associated with various anti-diabetic medications reported in a recent meta-analysis [5]. This finding that a small magnitude of weight loss was associated with regression to NGT is consistent with the findings of the Diabetes Prevention Program, which found that there is a strong relationship between weight loss and subsequent incident T2DM among people at high risk of T2DM [24]. This raises questions about how this degree of body size reduction can be achieved. Physician referral to a commercial weight loss programme can result in a one year mean weight loss of around 8% [25]. A multitude of weight loss clinical trial data suggest that 5-9% weight loss can be achieved through real world reduced-energy diets and exercise, with some additional benefit of weight-loss medications [26]. In our study, participants received minimal intervention, namely a leaflet promoting the benefits of a healthy lifestyle. This, combined with the knowledge that they were at higher risk of developing T2DM, appears to have encouraged weight loss in some participants, with 3% being the median weight loss observed at one year among those who lost weight, though regression to the mean could also explain this. This suggests that this moderate weight loss is achievable and is a realistic goal to set in a clinical setting, though it is slightly lower than that currently recommended in some guidelines [27]. Furthermore, this level of weight loss can be achieved when diabetes prevention interventions are implemented in a pragmatic manner [6].

Changes in physical activity, alcohol consumption and statin use were not associated with regressing to NGT. This might be because these variables were assessed by imprecise self-report measures that may be subject to social desirability bias [28], or may not be sensitive to change at the individual level [29]. Associations were generally in the expected direction but small, therefore the study may not have been sufficiently powered to detect changes in these variables. Further investigation is therefore required before conclusions can be drawn regarding the effect of these variables on regression to NGT.

Unsurprisingly, BMI, waist circumference and glucose indices were higher at baseline in the non-regression (sustained IGR or developed T2DM) group, indicating fat mass driven insulin resistance and glucose concentration are predictors of diabetes in our study population. In the Diabetes Prevention Programme Outcomes Study, both regression and IGR groups were well matched for BMI and treatment modality, suggesting improved beta cell function may relate directly to observed glucose lowering [16]. In our study, NGT remained an independent determinant of incident diabetes in a multivariate model adjusting for BMI, family history of diabetes, physical activity and other factors. Aggressive initial management of glucose has been associated with a recovery effect on subsequent beta cell function, which may be sufficient to influence treatment course in newly diagnosed modest hyperglycaemia [30, 31].

This study has notable strengths, such as the inclusion of a multi-ethnic cohort based on the WHO definition of intermediate hyperglycaemia and with only 75g-OGTT data included in our definition of IGR, which it has been argued is a preferable approach [32]. Furthermore, we included HbA_{1c} in the definition of T2DM as a sensitivity analysis, in line with current WHO recommendations [21], and this did not change our conclusions. This was an

observational cohort study recruited from a community population, so the results were not due to a particular treatment regime, and are more generalisable than data from highly selected populations in randomised controlled trials. These data convey an important public health message that people who achieve modest weight loss within a year of IGR diagnosis are approximately twice as likely to regress to a metabolic state associated with a significantly lower risk of diabetes and cardiovascular disease. Given the high prevalence of IGR, it is important to emphasise the effectiveness of lifestyle modification in this condition; our observations provide new information that will reinforce informed decision making and target-driven change in this regard. As screening for T2DM is now widespread and endorsed by many health authorities, increased identification of accepted IGR ranges is inevitable, which is as an opportunity to reach high risk cases with undisputedly effective interventions.

Limitations of this study should be considered when interpreting its findings. First, participant loss to follow-up, particularly towards the end of the study, could have introduced ascertainment bias. Whilst acknowledging this as a potential source of error, non-attendee characteristics were nearly identical to those individuals completing the study and there was no evidence that reverting to NGT at one year influenced subsequent return rate. Second, this study was not designed to explore the pathophysiological basis of any relationship between early glucose lowering and incident diabetes. A second baseline 75g-OGTT may have re-classified some borderline cases of IGR, and it could be argued that these individuals actually have NGT [33]. Whilst acknowledging a lack of confirmatory testing for non-diabetes range glucose dysregulation as a limitation of our study, sensitivity analyses excluding participants close to diagnostic thresholds for NGT at baseline did not

substantially change the results, except that some results were no longer significant (Supplementary Tables 3 and 4). It therefore seems unlikely that we are simply observing baseline variability in the 75g-OGTTs of individuals with lower rates of progression to diabetes. Presumably, if variability in glucose testing was the sole reason for regression then we would not expect to see such a strong link with T2DM outcomes as observed in the current study. Third, this observational work does not infer causality. Relationships between body mass change and regression to NGT could have occurred by chance and can only be definitely tested in controlled intervention studies. Trial data do exist for weight loss and regression to NGT from the Diabetes Prevention Program, which also suggests that such regression conveys additional cardiovascular benefits since any degree of dysglycaemia can have adverse effects [15, 16]. Whilst these data provide evidence of a causal association, to our knowledge there are no such data in other settings and populations. Finally, the study may have been underpowered to detect some associations but due to the large effect sizes many of these were highly statistically significant and there was almost no bias in those lost to follow-up. Measurement of some of the modifiable risk factors could have been improved upon.

We have confirmed that early regression from intermediate hyperglycaemia to NGT is associated with reduced diabetes incidence, and extended these results into a non-intervention setting that has greater generalisability than previous studies. Our findings provide new evidence that reductions in body size may be the most important factor for increasing the chance of regression to NGT. A simple message for those identified with intermediate hyperglycaemia or “prediabetes” could be that if they achieve any degree of weight loss within one year then they are twice as likely to achieve NGT. Finally, rates of

progression and regression appear comparable with other historical data and should provide important contemporary information for health care planners involved in diabetes prevention.

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Table 1. Baseline descriptive characteristics of the 817 participants included in the analysis overall and by glycaemic status at one year

Variable	All	Glycaemic status at one year		p-value ^a
		Did not regress	Regressed to NGT	
		Mean (Standard deviation)		
Age, years	59.9 (10.0)	60.6 (9.7)	59.3 (10.2)	0.065
Fasting glucose, mmol/l	5.6 (0.7)	5.8 (0.7)	5.5 (0.6)	<0.001
2 hour glucose, mmol/l	8.6 (1.7)	8.9 (1.8)	8.4 (1.5)	<0.001
HbA _{1c} , mmol/mol	40 (4.4)	42.0 (5.5)	40.0 (4.4)	<0.001
HbA _{1c} , %	5.9 (0.4)	6.0 (0.5)	5.8 (0.4)	<0.001
Waist circumference, cm	98.3 (13.0)	100.5 (13.4)	96.5 (12.4)	<0.001
Weight, kg	81.5 (16.2)	83.6 (17.3)	79.8 (15.1)	0.002
Social deprivation score	19.9 (13.6)	20.1 (13.3)	19.7 (13.8)	0.728
n (%)				
Sex				
Male	384 (47.0)	179 (47.6)	205 (46.5)	0.749
Female	433 (53.0)	197 (52.4)	236 (53.5)	
Ethnicity				
White European	498 (61.0)	215 (57.2)	283 (64.2)	0.239
South Asian	176 (21.5)	88 (23.4)	88 (20.0)	
Other	20 (2.5)	10 (2.7)	10 (2.3)	
Missing	123 (15.1)	63 (16.8)	60 (13.6)	
Baseline diagnosis				
IFG	146 (17.9)	73 (19.4)	73 (16.6)	<0.001
IGT	558 (68.3)	221 (58.8)	337 (76.4)	
Both	113 (13.8)	82 (21.8)	31 (7.0)	
Smoking status				
Never smoker	424 (51.9)	191 (50.8)	233 (52.8)	0.754
Ex-smoker	206 (25.2)	94 (25.0)	112 (25.4)	
Current smoker	58 (7.1)	26 (6.9)	32 (7.3)	
Missing	129 (15.8)	65 (17.3)	64 (14.5)	
Body mass index				
Normal	110 (13.5)	40 (10.6)	70 (15.9)	0.004
Overweight	295 (36.1)	121 (32.2)	174 (39.5)	
Obese	284 (34.8)	150 (39.9)	134 (30.4)	
Missing	128 (15.7)	65 (17.3)	63 (14.3)	
Family history of diabetes				
No	511 (62.6)	224 (59.6)	287 (65.1)	0.105
Yes	306 (37.5)	152 (40.4)	154 (34.9)	
Total		376 (100.0)	441 (100.0)	

Abbreviations: IFG, Impaired Fasting Glucose; IGT, Impaired Glucose Tolerance; NGT,

Normal Glucose Tolerance; T2DM, Type 2 Diabetes Mellitus.

Missing values: Age and Fasting Glucose, 0; 2-hour glucose, 2; HbA_{1c}, 6; Waist circumference, 126; Weight, 128; Social deprivation score, 24.

^a p-values test for a difference between the glycaemic groups at one year and were estimated using t-tests for continuous variables and chi-squared tests for categorical variables.

Table 2. The association between changes in modifiable risk factors from baseline to one year and regression to normal glucose tolerance.

Variable	n (%)		Adjusted OR (95% CI) of regressing ^a	p-value
	Did not regress (n=376)	Regressed to NGT (n=441)		
<i>Weight</i>				
Same or gained	172 (49.4)	176 (50.6)	Referent	
Lost 0.1-3%	36 (32.1)	76 (67.9)	1.81 (1.08, 3.03)	0.025
Lost >3%	57 (39.9)	86 (60.1)	1.30 (0.81, 2.09)	0.271
<i>Waist circumference</i>				
Same or gained	203 (46.8)	231 (53.2)	Referent	
Lost 0.1-3cm	29 (38.2)	47 (61.8)	1.15 (0.65, 2.02)	0.634
Lost >3cm	33 (34.4)	63 (65.6)	1.78 (1.03, 3.06)	0.037
<i>Walking, minutes</i>				
No change or decreased	40 (38.1)	65 (61.9)	Referent	
Increased	61 (35.9)	109 (64.1)	0.96 (0.54, 1.71)	0.900
<i>Moderate PA, minutes</i>				
No change or decreased	23 (36.5)	40 (63.5)	Referent	
Increased	64 (35.4)	117 (64.6)	0.79 (0.38, 1.62)	0.513
<i>Vigorous PA, minutes</i>				
No change or decreased	18 (34.6)	34 (65.4)	Referent	
Increased	73 (34.3)	140 (65.7)	0.76 (0.35, 1.67)	0.494
<i>Alcohol units consumed per week</i>				
No change or increased	30 (30.9)	67 (69.1)	Referent	
Decreased	45 (37.5)	75 (62.5)	0.63 (0.34, 1.18)	0.149
<i>Statins</i>				
Not prescribed at all	300 (46.2)	349 (53.8)	Referent	
Started between baseline & follow-up	19 (38.8)	30 (61.2)	1.03 (0.47, 2.27)	0.942
Taking at baseline	57 (47.9)	62 (52.1)	0.96 (0.60, 1.56)	0.881

Abbreviations: CI, Confidence Interval; NGT, Normal Glucose Tolerance; OR, Odds Ratio; PA,

Physical Activity.

^a Adjusted for age, sex, ethnicity, social deprivation score, baseline diagnosis (i.e. impaired fasting glucose, impaired glucose tolerance, or both), body mass index, family history of diabetes, and physical activity (total METS per week).

Table 3. Risk of incident type 2 diabetes mellitus for those who regressed to normal glucose tolerance compared with those who remained with impaired glucose regulation at first follow-up.

	Unadjusted (N = 630)	Model 1 (N = 521)	Model 2 (N = 521)	Model 3 (N = 420)
Glycaemic status at one year				
Did not regress	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
Regressed to NGT	0.20 (0.12, 0.33)	0.18 (0.10, 0.31)	0.21 (0.12, 0.37)	0.19 (0.10, 0.37)
Age, years		0.99 (0.96, 1.01)	0.99 (0.96, 1.01)	1.00 (0.97, 1.04)
Sex				
Men		1 (Reference)	1 (Reference)	1 (Reference)
Women		1.03 (0.64, 1.67)	1.26 (0.77, 2.07)	1.07 (0.59, 1.95)
Ethnicity				
White		1 (Reference)	1 (Reference)	1 (Reference)
Non-White		1.22 (0.69, 2.15)	1.28 (0.72, 2.27)	1.67 (0.79, 3.53)
Social deprivation score		1.01 (0.99, 1.02)	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)
Baseline diagnosis				
IFG only			1 (Reference)	1 (Reference)
IGT only			0.84 (0.41, 1.71)	1.10 (0.49, 2.43)
Both IFG and IGT			3.85 (1.87, 7.90)	3.81 (1.65, 8.79)
Body mass index, kg/m ²				1.07 (1.01, 1.13)
Family history of diabetes				
No				1 (Reference)
Yes				0.86 (0.46, 1.62)
Physical activity, total METS/week				1.00 (1.00, 1.00)
Change in weight from baseline to one year, %				1.05 (0.98, 1.11)

Abbreviations: CI, Confidence Interval; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; HR, Hazard Ratio; NGT, Normal Glucose Tolerance.

Figure Legends

Figure 1 legend.

Flowchart showing the progress of participants through the ADDITION-Prediabetes Cohort Study. Abbreviations: IFG, Impaired Fasting Glycaemia; IGT, Impaired Glucose Tolerance.

Figure 2 legend.

Kaplan-Meier graph showing the incidence of type 2 diabetes stratified by glucose status at one year (regressed to normal glucose tolerance (NGT) vs remained with impaired glucose regulation (IGR)).