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Long-term remission of impaired glucose tolerance in the finnish diabetes prevention study

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ABSTRACT

Aims: Lifestyle interventions induce remission in people with type 2 diabetes (T2D) and those with impaired glucose tolerance (IGT). We examined the long-term remission of IGT in the participants of the Finnish Diabetes Prevention Study and evaluated factors predicting remission during extended follow-up.
Methods: 505 participants were included in analyses. The median duration of lifestyle intervention was four years, and follow-up lasted up to 18 years. Remission was defined as normoglycaemia (fasting plasma glucose < 5.6 mmol/L, 2-h post-load glucose < 7.8 mmol/L, HbA1c < 39 mmol/mol). We examined predictors of remission (weight, fat distribution, physical activity, diet, and insulin sensitivity and insulin secretion based on repeated oral glucose tolerance tests).
Results: Remission rates were 32% at least once, 13%, 12%, and 11% at year 1, year 3, and the first post-intervention follow-up visit (median 5 years, range 4 – 8 years). Short-term predictors of remission included weight loss, reduction in waist circumference, higher intake of fibre and lower intake of saturated fats, physical activity, enhanced insulin sensitivity, and recovery of insulin secretion. In the longer term, only insulin secretory and sensitivity indices were associated with remission.
Conclusion: IGT may be normalised in the long term through weight loss and healthier lifestyles choices.

1. Introduction

Since the late 1990s, many well-controlled intervention studies have proven that it is possible to slow or prevent the progression from IGT to T2D, especially among people with overweight or obesity, through healthy dietary choices and increased physical activity, leading to weight reduction [1–4]. The landmark DiRECT (Diabetes Remission Clinical Trial) study demonstrated that people with recently diagnosed T2D can achieve remission, defined as maintaining blood glucose levels in a non-diabetic range without the need for glucose-lowering medications, through a tight dietary programme involving total diet replacement [5]. The remission rate was strongly correlated with the degree of weight loss.

Following the publication of the DiRECT study results, other studies have investigated remission in individuals with recently diagnosed T2D [6,7] and also in those with prediabetes [8]. A recent systematic review and *meta*-regression analysis [7], including 22 randomised trials on people with T2D, found that weight loss achieved with lifestyle modification (six studies included), bariatric surgery, or anti-obesity drugs resulted in complete remission of diabetes after one year. The probability of reaching complete remission increased by two percentage points for every one percentage point decrease in body weight. Remission occurred in 21.7% of participants who lost at least 10% of their body weight, increasing to 43.4% and 65.1% among those who lost more than 20% and 30%, respectively. However, these remission rates decreased substantially beyond the 1-year follow-up period [7].

Evidence that people with T2D can enter remission has prompted researchers to investigate whether IGT can similarly revert to normal glucose regulation [8–19]. Reported remission rates have varied considerably across these studies, and secondary analyses have typically compared responders and non-responders, often categorised by the degree of body weight reduction. In the US DPPOS (Diabetes Prevention

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Program Outcomes Study), lifestyle-induced remission and weight loss were associated with a significantly lower risk of developing T2D. However, only 24% of 480 individuals who achieved a weight-loss target of at least 7% attained remission [10].

Recent 5-year follow-up results from the DiRECT study further support the feasibility of long-term remission of T2D. Among participants in remission at year 2, 26% (27% vs. 4% in the former intervention and control groups, respectively) remained in remission at the 5-year follow-up examination, where the remission criterion was HbA1c < 48 mmol/mol. However, only 85 of the original 149 participants in the intervention group took part in the follow-up programme [11]. To extend our understanding of the remission phenomenon, its contributing factors, and potential underlying mechanisms, we assessed remission from IGT to normoglycaemia among participants of the Finnish Diabetes Prevention Study (DPS) with a median follow-up of 5 years (range 4–8 years), and a maximum of 18 years from baseline regarding the association of the incidence of T2D with remission status [12,13]. In addition to the changes in anthropometry, we also evaluated the effects of lifestyle factors on remission. We also explored longitudinally underlying physiological mechanisms potentially associated with remission, analysing annually or biennially indices of insulin secretion and sensitivity (1 to 9 measurements), since previous remission studies in people with prediabetes have not fully identified the mechanisms responsible for long-term remission, which remains to be elucidated.

2. Methods

The DPS was the first proper, individually controlled lifestyle intervention trial to demonstrate that T2D can be prevented by weight reduction, healthy dietary choices, and increased physical activity [2,12,13]. The DPS was carried out in five centres in Finland, enrolling 522 people with IGT aged 40–64 years between November 2, 1993, and May 4, 1998. The oral glucose tolerance test (OGTT) was repeated in individuals whose first 2-hour plasma glucose values were abnormal, and the mean of the two values was used to determine eligibility. Criteria for exclusion were a diagnosis of diabetes mellitus, the presence of chronic disease that rendered survival for six years unlikely, and other characteristics (psychological or physical disabilities) deemed likely to interfere with participation in the study. Participants were randomly allocated to the intervention and control (usual care) groups. The active intervention period lasted a median of four years, after which participants were followed for up to nine years (median follow-up of 8 years) without further active intervention [12,13]. Later, new cases of T2D were identified from Finnish health register data. Participants in the intervention group were repeatedly provided with individualised guidance and support to achieve a healthy diet, increased physical activity, and to lose weight. In contrast, those in the control group received only general information about healthy lifestyles.

An OGTT was repeated annually during the early years of the study and biennially thereafter until 2013, or until a diagnosis of T2D or participant dropout. The present study population comprised 505 individuals who had consented to the follow-up analyses. Detailed descriptions of the methods, clinical characteristics, and physiological and biochemical measurements have been previously reported in detail [2,12,13]. A 2-hour OGTT was performed in the fasting state in the morning using a 75 g glucose load, and plasma glucose and serum insulin samples were collected at 0, 30, 60, and 120 min after glucose ingestion. Insulin sensitivity (Matsuda index), disposition index, and first-phase secretion indices: amended insulin-to-glucose ratio (AIGR) and adjusted AIGR) were calculated using the standard methods as described previously [14,15]. Samples for 30-min insulin analyses during OGTTs were not collected before 1996; therefore, baseline data were not available for all participants [14]. Variables reflecting insulin sensitivity and insulin secretion were selected based on findings from a large Finnish population-based study and were validated accordingly [15]. In this study, remission of IGT was defined as normoglycaemia – fasting plasma glucose < 5.6 mmol/L, 2-h post-load glucose < 7.8 mmol/L, and HbA1c < 39 mmol/mol – without the use of glucose-lowering medication.

Importantly, we also analysed the potential impact of diet quality and physical activity on remission outcomes. Dietary intakes were assessed using 3-day food records obtained at baseline and annually during the intervention phase and at the 1- and 4-year follow-up visits. Dietary goals for the intervention group were total fat < 30% of total energy, saturated fat < 10% of total energy, and fibre ≥ 15 g /1000 kcal. The goal for total moderate-intensity physical activity was at least four hours per week. Compliance with each recommendation was coded as a binary variable (0 = not achieved, 1 = achieved) to examine its association with the incidence of remission [12,13]. The number of study visits per person ranged from 1 to 15.

In the present study, diabetes diagnosis was based either on OGTTs conducted during the 18-year follow-up period (median 8 years) or from the national Finnish health registers (Prescription database, Special Reimbursement Register for Drug Costs, Care Register for Health Care, and Causes of Death Statistics) with up to 25 years of follow-up (median 12 years). A total of 257 and 248 individuals from the original intervention and control groups, respectively, consented to record linkage with these national health registries. Register-based data were used to analyse the long-term effects of remission on the incidence of new-onset diabetes.

2.1. Ethical approval

The study protocol was approved by the Ethics Committees of the National Public Health Institute in Helsinki, Finland (intervention phase), and of the North Ostrobothnia Hospital District (follow-up period). All study participants provided written informed consent at baseline and again at the beginning of the post-intervention follow-up. The trial was registered in ClinicalTrials.gov NCT00518167. The trial protocol and any other materials can be accessed at the Finnish Institute for Health and Welfare via one of the authors (JL).

2.2. Statistical analysis

We analysed the association of remission status with (i) insulin function indices (Matsuda ISI, AIGR, adjusted AIGR, and Disposition index) (DI), (ii) anthropometric measurements (body weight, waist circumference, and sagittal abdominal diameter), and (iii) lifestyle factors (total fat intake (not reported), saturated fatty acid intake, dietary fibre intake, and physical activity). Associations were modeled using mixed-effects logit models with random intercepts for individual study participants. Each risk factor was analysed in a separate model, adjusting for relevant confounders; models for anthropometric and lifestyle factors were adjusted for sex, age at baseline, and intervention allocation group, and models involving insulin indices were additionally adjusted for weight loss. Before the analysis, the insulin function indices were standardised at each time point to allow direct comparison of their effect sizes and their relative importance in predicting remission. Lifestyle factors were coded as binary (0 = not achieved, 1 = achieved) based on whether the recommended intervention targets were met. Observations after a T2D diagnosis were excluded from the analyses. The analyses were performed as complete-case analyses, including all data points with measurements of remission and the predictor, and excluding those with missing values. Across all study visits up to a possible T2D diagnosis, remission status was missing in 12% of the visits.

We performed two types of analyses. First, in the concurrent analyses, risk factor values and remission status were assessed at the same points using all available measurements for each participant before T2D diagnosis. Second, in the predictive analyses, risk factor values from the first three years were used to predict remission status during the post-intervention follow-up period. For insulin function indices (Matsuda

ISI, disposition index, AIGR, and adjusted AIGR), mean values over the first three years were used. For the anthropometric variables (body weight, waist circumference, and sagittal abdominal diameter), changes from baseline to the third study visit were used. Lifestyle factor values (diet, physical activity), measured at the third annual visit, served as predictors.

The associations between the remission status and the subsequent risk of developing T2D were assessed using the Nelson-Aalen cumulative hazard functions. Three analyses were performed using different starting time points for the follow-up (1-year visit, 3-year visit, or the first post-intervention follow-up visit). For each analysis, the remission status was determined at the starting time, and the individuals were followed until the earliest of the following events: T2D diagnosis, death, or the administrative end of study (December 31, 2018) (Fig. 1). A total of 40 individuals without a T2D diagnosis died during the study period. We also fitted Cox proportional hazards models to statistically test differences in the cumulative hazard curves. However, the proportional hazards assumption was not met, meaning that the estimated hazard ratios could not be interpreted as time-constant effects. Inverse probability weighting was used to adjust the cumulative hazard curves and Cox models for sex, baseline age, and intervention allocation group. Interaction terms were included in the Cox models to assess potential effect modification by intervention allocation status.

The statistical analyses were conducted using R software, version 4.4.11 [16]. The Nelson-Aalen curves and Cox models were fitted using the package survival, version 3.7.0 [17], and the mixed-effects logit

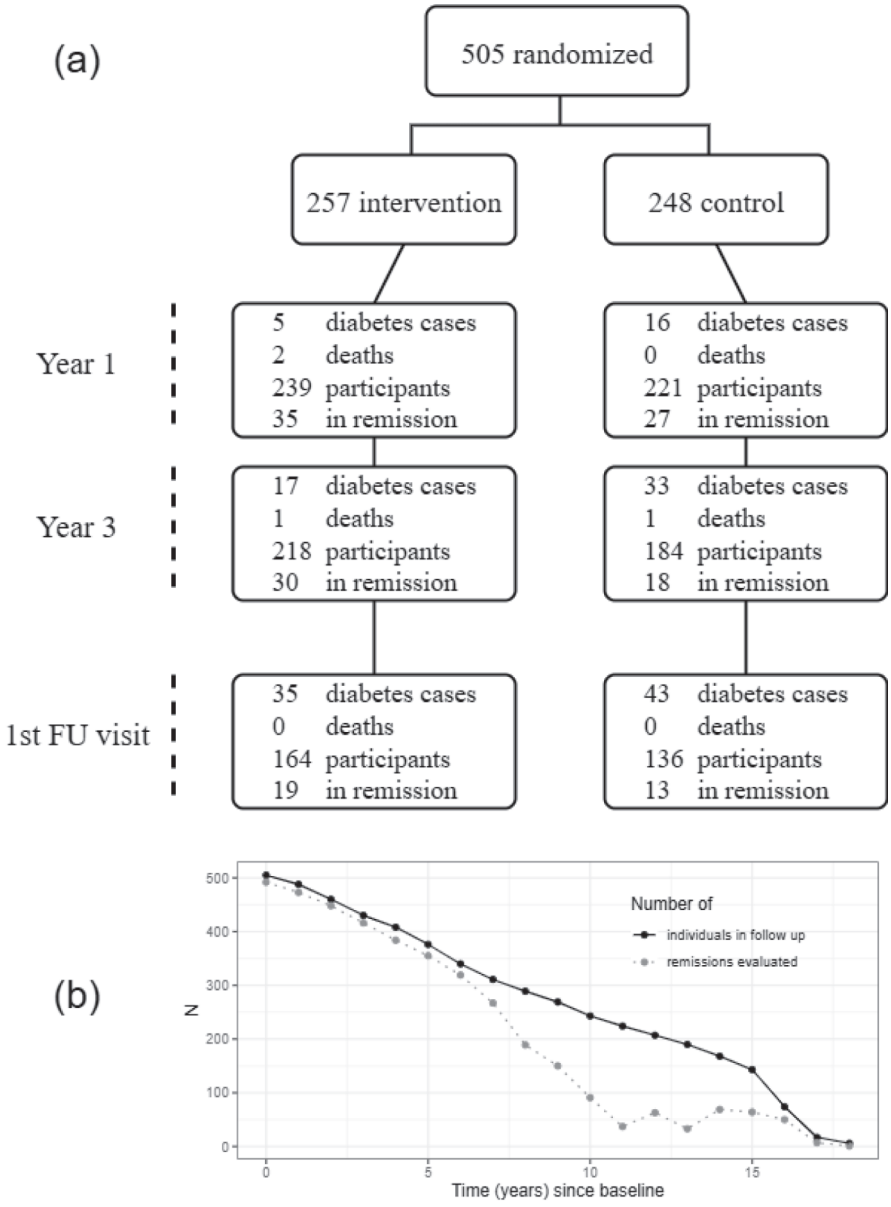

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Fig. 1. Fig. 1. (a) Formation of the study population: the numbers of new diabetes cases and deaths, and the numbers of remaining participants and those in remission at the 1-year, 3-year and the first post-intervention follow up visits. (b) The number of individuals considered remaining in the follow up after each year and the number of available measurements of remission.

models using the package lme4, version 1.1.35.5 [18]. A p-value of less than 0.05 was considered statistically significant.

2.3. Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. Results

The original study population of DPS included 522 patients with IGT and overweight or obesity, aged 40 to 64 years. As shown previously, weight loss was greater in the intervention group than the control group from year 1 through to the end of the 13-year follow-up. Also, the incidence of diabetes was lower in the intervention group than the control group (relative risk reduction 58% at four years and 40% after 13 years) [2,13]. Fig. 1 shows the formation of the current study population, comprising participants who agreed to include their follow-up data in the analysis of the study. Median of the total follow-up time was 8 years (range 0–18 years) and the median number of study visits was 9 (range 1–15).

Table 1 presents the selected baseline characteristics of the participants, stratified by remission status during the follow-up. Overall, 162 of 505 (32%) study participants experienced remission at least once during the entire follow-up period. Remission rates to normoglycaemia in the total study population were 13% (N = 62), 12% (N = 48), and 11% (N = 32), at year 1, at year 3, and at the first post-intervention study visit (median 5 years, range 4–8 years), with no statistically significant difference in remission rates between the intervention and control groups. Among those who experienced remission at least once, the median time of first remission was 1 year with interquartile range (IQR) between 1 and 3 years since baseline, and in the median proportion of the study visits a study participant observed in remission was 22% with IQR 11% to 33%.

Averaging over the entire follow up, the proportion of the participants in remission was 9% among those who were not in remission at the previous visit, compared with 35% among those in remission at the previous visit. Remission at least once was more frequent in the first (lowest) tertiles of baseline fasting and 2-h plasma glucose values. Using the first tertile as reference, the odds ratios (95% CI) for fasting plasma glucose were 0.26 (0.16–0.42) and 0.06 (0.03–0.11) for the second and third tertiles, respectively, and for 2-h glucose these odds ratios were 0.41 (0.26–0.65) and 0.21 (0.12–0.35), respectively. Respective odds ratios according to the tertiles for the long-follow-up remission were numerically almost identical to these “at least once” remission figures.

T2D incidence was lower among individuals at remission than those not in remission. Evaluating the remission status and starting the follow up at year 1, year 3 and the first post-intervention follow up, the hazard ratios (95% CI) were 0.41 (0.28–0.60, $p < 0.001$), 0.40 (025–0.63, $p < 0.001$) and 0.20 (0.08–0.49, $p < 0.001$), respectively. Fig. 2 shows the cumulative hazards of developing T2D, stratified by remission status at each starting time point. Throughout the entire follow-up, remission was associated with a long-term reduction of T2D risk. No statistically significant interaction was found between remission status and the intervention group assignment.

Table 2 shows the odds ratios for remission associated with various predictors measured at the same time point as remission status. Among the standardised insulin indices, the disposition index had the strongest association with remission (OR 3.20; 95% CI 2.67–3.85), suggesting it was the best indicator for distinguishing individuals in remission. The ORs for Matsuda ISI (2.66; 95% CI 2.24–3.17) and adjusted AIGR (2.76; 95% CI 2.29–3.32) were comparable, while the AIGR had a weaker but statistically significant association (1.58; 95% CI 1.30–1.91). All the anthropometric variables were statistically significant predictors of remission. The odds for remission increased with a greater weight loss, being 2.37 (95% CI 1.69–3.32) for individuals achieving at least 5% weight loss and 2.76 (95% CI 1.91–3.99) for those achieving at least 7% weight loss. Among lifestyle factors, reaching the goal for saturated fat intake (OR 1.55; 95% CI 0.997–2.41), dietary fibre intake (OR 1.55; 95% CI 1.06–2.27), and physical activity (OR 1.52; 95% CI 1.06–2.18) were directly associated with remission. An additional adjustment for baseline HbA1c resulted in loss of significance of lifestyle-related factors (data not shown).

When examining predictors over the first three years in relation to remission during the post-intervention follow-up, only the disposition index, Matsuda ISI, and adjusted AIGR were statistically significant. Again, the disposition index showed the strongest association of the standardized insulin indices (2.35; 95% CI 1.66–3.34), followed by equal estimates for adjusted AIGR (1.96; 95% CI 1.4–2.74) and Matsuda ISI (1.85; 95% CI 1.31–2.61), and the lowest for AIGR (1.33; 95% CI 1.00–1.86). Among lifestyle factors, only physical activity was a significant predictor of remission (OR 2.80; 95% CI 1.09–7.17); however,

Table 1
Baseline characteristics of the study population according to remission status and the corresponding averages and standard deviations over the observed follow-up.

		No remission observed at any time		Observed at remission during the follow up§	
		Baseline	Study visits average	Baseline	Study visits average
N (male/female)		343 (114/229)	6 (3–11)*	162 (52/110)	13 (10–13)*
Age at baseline (years)		55 (7.02)		55.7 (7.31)	
BMI (kg/m^2)	Male	30.0 (3.35)	29.7 (3.50)	29.8 (4.08)	29.0 (3.97)
	Female	32.4 (5.00)	32.0 (5.13)	30.9 (4.27)	30.1 (4.25)
Fasting plasma glucose (mmol/l)		6.37 (0.721)	6.4 (0.577)	5.65 (0.575)	5.72 (0.365)
2-h plasma glucose (mmol/l)		9.17 (1.47)	8.95 (1.28)	8.29 (1.34)	7.77 (0.928)
HbA1c (mmol/mol)		39.0 (6.83)	39.1 (5.02)	35.8 (4.27)	34.9 (3.33)
Fasting serum insulin (pmol/l)**		64.7 (47.4–87.8)	68.2 (54.0–91.2)	50.8 (38.1–73.9)	57.0 (42.8–75.1)
2-h serum insulin (pmol/l)**		397 (273–554)	406 (288–575)	333 (221–504)	339 (238–564)
Matsuda ISI†		3.20 (1.81)	3.78 (2.09)	4.16 (2.32)	5.14 (2.33)
AIGR (0–30 min) †***		21.3 (13.2)	23.4 (12.1)	25.5 (14.4)	27.8 (12.5)
Adjusted AIGR†,***		18.8 (9.10)	20.4 (8.05)	25.4 (10.2)	27.3 (9.11)
Disposition index		48.9 (12.6)	67.5 (36.1)	77.5 (25.2)	104 (41.0)

§At year 1, 15% of participants in the intervention and 12% in the control group had normal glucose metabolism; at year 3, the respective figures were 14% and 10%, and at the first post-intervention follow-up visit, 12% and 10%.
* Number of study visits per person; median (interquartile range).
** Tabulated as median (interquartile range)*** Values from the first study visit when these values were available.
† *Matsuda ISI denotes insulin sensitivity index. AIGR denotes the first phase (30* min*) insulin secretion capacity, and adjusted AIGR denotes the value adjusted for Matsuda ISI (Ref. 25).*

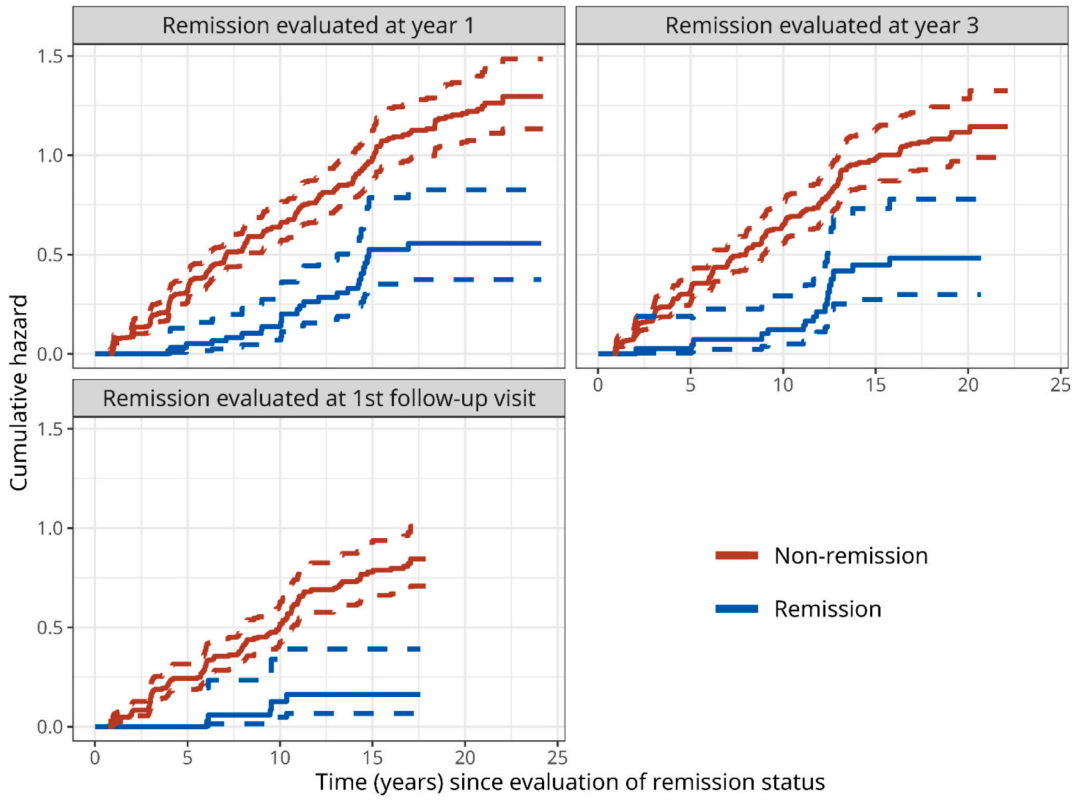

Fig. 2. Nelson-Aalen cumulative hazards and their 95% confidence intervals for T2D among individuals in remission and those not in remission at the specified starting times. Three separate analyses were conducted, starting the follow-up at year 1, year 3 or the first post-intervention follow-up visit. The remission status was evaluated at the starting time and individuals followed until T2D diagnosis, death, or the administrative end of study (December 31, 2018). The curves were weighted after adjusting for sex, age at baseline, and intervention allocation group.

Table 2
Associations between the predictors and remission status were evaluated at the same time point. The analyses were conducted using mixed effects logistic regression models with individual-level random intercepts. The models with predictors related to obesity and lifestyle variables were adjusted for sex, age at baseline, and intervention allocation group. The remaining models were additionally adjusted for the relative weight change as a continuous measure.

Predictor	Odds Ratio	95% Confidence interval	p	N observations*	N individuals*	N remissions*
Matsuda ISI**	2.66	2.24–3.17	<0.001	3452	500	377
AIGR***	1.58	1.30–1.91	<0.001	2607	437	317
adj AIGR***	2.76	2.29–3.32	<0.001	2578	434	314
Disposition Index	3.20	2.67–3.85	<0.001	2578	434	314
Weight loss over 5%	2.37	1.69–3.32	<0.001	3197	475	375
Weight loss over 7%	2.76	1.91–3.99	<0.001	3197	475	375
Sagittal abdominal diameter decrease (cm)	1.24	1.15–1.35	<0.001	3605	500	389
Waist circumference decrease (cm)	1.13	1.10–1.16	<0.001	3665	502	401
Intake of saturated fatty acids <10 energy%	1.55	0.997–2.41	0.052	2169	502	247
Intake of dietary fibre ≥ 15 g/1000 kcal of energy intake	1.55	1.06–2.27	0.026	2169	502	247
Physical activity ≥4 h/week	1.52	1.06–2.18	0.023	3461	502	370
Intervention allocation group	1.36	0.859–2.14	0.192	3696	504	404

* 'N observations': the total number of observed predictor–outcome pairs; 'N individuals': the number of study participants included in each model; 'N remissions': the number of observed remissions at each time point of observation.
** Matsuda ISI denotes insulin sensitivity index.
*** AIGR denotes the first-phase (30 min) insulin secretion capacity, and adjusted AIGR denotes the value adjusted for Matsuda ISI (Ref. 25).

the relatively large point estimate combined with a wide confidence interval warrants caution in interpretation (Table 3).

4. Discussion

In the present study, based on the long-term follow-up of the DPS, we found that 32% of the participants with IGT achieved normoglycaemia at least once during the follow-up, and 13%, 12%, and 11% at year 1, year 3, and at the first post-intervention follow-up visit, respectively. Factors associated with remission were weight reduction, decreased waist circumference and sagittal abdominal diameter, low intake of saturated fatty acids, increased dietary fibre intake, and increased physical activity. The current results tend to confirm that both better insulin sensitivity and long-term recovery of insulin secretion capacity contribute to remission, partly independent of weight loss and lifestyle factors. Our study provided novel results showing that normalisation of glucose metabolism in people with IGT is associated with diet and physical activity in a shorter term. We also confirmed that remission in

Table 3
The associations between early changes in the predictors and the remission status were assessed during the follow-up. Predictors representing change since baseline were evaluated at the three-year visit, whereas predictors representing an average were calculated as a mean of the baseline visit and visits over the first three years. Analyses were conducted using mixed effects logistic regression models with individual-level random intercepts. Models including anthropometric or lifestyle predictors were adjusted for sex, age at baseline, and intervention allocation group. The remaining models were additionally adjusted for the relative weight change at the first follow-up visit.

Predictor	Odds Ratio	95% Confidence interval	p	N observations*	N individuals*	N remissions*
Matsuda ISI** (0–3y average§)	1.85	1.31–2.61	<0.001	1347	306	142
AIGR*** (0–3y average)	1.33	0.955–1.86	0.091	1215	270	127
adj AIGR*** (0–3y average)	1.96	1.40–2.74	<0.001	1215	270	127
Disposition Index	2.35	1.66–3.34	<0.001	1215	270	127
3y weight loss over 5%	1.48	0.672–3.26	0.330	1348	308	142
3y weight loss over 7%	1.16	0.481–2.77	0.748	1348	308	142
3y sagittal diameter decrease (cm)	1.09	0.897–1.33	0.377	1332	302	141
3y waist circumference decrease (cm)	1.01	0.949–1.08	0.674	1329	302	140
Intake of saturated fatty acids < 10 energy %	1.05	0.386–2.85	0.927	1357	312	142
Intake of dietary fibre ≥ 15 g/1000 kcal of energy intake	1.08	0.481–2.41	0.859	1357	312	142
Physical activity ≥ 4 h per week	2.80	1.09–7.17	0.032	1357	312	142

* 'N observations': the total number of observed predictor–outcome pairs; 'N individuals': the number of study participants included in each model; 'N remissions': the total number of observed remissions at each time point.
** Matsuda ISI denotes insulin sensitivity index.
*** AIGR denotes the first-phase (30 min) insulin secretion capacity, and adjusted AIGR denotes the value adjusted for Matsuda ISI (Ref. 25).
§ 0-3y average denotes average values from baseline to 3-year examination.

people with IGT significantly reduces the incidence of T2D.

Remission of T2D has gained considerable attention following the publication of the DiRECT study [5]. This one-year intensive weight reduction programme demonstrated that remission of T2D (HbA1c < 48 mmol/mol) was possible in many individuals with recently diagnosed T2D and obesity. However, the remission rate was substantially lower at the 5-year follow-up, which included only a subset of the original participants [11]. A recent *meta*-analysis of 15 studies involving individuals with T2D who underwent various weight reduction interventions—including bariatric surgery—reported an average overall remission rate of 14.4% (range: 6.1%–25.0%) after five years of follow-up. In contrast, three lifestyle intervention studies involving 464 individuals with T2D reported an average remission rate of only 7% [7].

Remission or temporary remission of T2D – defined as the return of glycaemia to near-normal glucose levels – has been replicated in many studies with various study designs and populations, including people with T2D or prediabetes in so-called real-life studies [6–8].' Results from these studies, published over the last 20 years, are consistent with earlier weight-reduction studies from the early 1990 s, although the term "remission" was not used at that time [19,20].

Among former DPS participants, the remission rate varied over the study period and averaged 11–13%. Overall, 32% achieved normoglycaemia at least once during the follow-up. We first reported the remission data up to 18 years, and extended the follow-up to 25 years, incorporating health register data on diabetes diagnoses into analyses of diabetes incidence (Fig. 2). Over this extended period, remission rates showed only limited variability. Not surprisingly, remission was associated with the baseline glycaemia, with more frequent remissions among people in the lower tertiles of fasting and 2-h plasma glucose values.

In the current study, the proportion of participants who achieved remission at least once during the follow-up was somewhat higher (32%) than in the DPPOS (23 – 25% depending on the randomisation group) [7,9,10,21]. However, participants with IGT in the DPPOS were generally more obese than those in the DPS. Over the long term, the remission rates in our study were comparable to those reported in DPPOS. [9,21]. In the DPS, the active intervention was discontinued at the end of the trial period, and no pharmacotherapy was prescribed; participants were followed only through periodic examinations and register linkage.

Weight reduction is the key determinant of improving glucose metabolism in people with prediabetes and T2D. It enhances insulin sensitivity and reduces hepatic glucose output [23,24]. Weight loss has been shown to restore insulin secretion capacity, as evidenced by improved insulin responses during oral or intravenous glucose tolerance tests [22–24,26]. Furthermore, weight reduction is associated with decreased liver fat content, abdominal and visceral adiposity, and pancreatic fat accumulation [21,23,24]. These changes in ectopic fat distribution may contribute both to enhanced insulin sensitivity and improved insulin secretion. It is important to note that energy restriction *per se* and weight loss may influence glucose metabolism through partly different mechanisms [25]. Lifestyle interventions that achieve weight loss may also improve peripheral glucose utilisation, a further component of the complex pathophysiology of T2D [25]. In the present study, remission over an median follow-up of 5 years (range 4–8 years) was associated with both enhanced insulin sensitivity and improved insulin secretion, as reflected by the disposition index and adjusted AIGR.

A recent study based on post hoc analyses of Prediabetes Lifestyle Intervention Study (PLIS) adds to our knowledge of the mechanisms of remission [(26]. In that study, remission was also reported in individuals without weight loss and was associated with improved insulin sensitivity and β-cell function in line with our present study and some earlier studies [22–24]. Furthermore, increases in β-cell-GLP-1 sensitivity were found in that study. Our results tend to confirm that insulin secretion may recover even without weight loss. The recent PLIS study results also suggested that fat distribution may significantly affect on the remission process since those without remission (non-responders) had an increase in visceral fat, whereas those with remission (responders) could even have an increase in subcutaneous fat mass [26].

In addition to weight loss, other lifestyle factors – such as physical activity and healthier eating habits [13] – may contribute to improved glucose tolerance and remission. In contrast to the PLIS post hoc analyses [26], in the present study both higher intake of dietary fibre and lower intake of saturated fatty acids, and higher levels of physical activity, were significantly associated with early remission. While findings are novel regarding prediabetes remission, they are consistent with our previous observations from the DPS, in which low intake of total and saturated fats and high dietary fibre intake were associated with a reduced risk of T2D [27]. The observed association between physical activity and remission aligns with our earlier DPS results, which demonstrated a marked reduction in T2D incidence among more physically active participants [28]. Our current findings extend these results

by demonstrating the long-term remission of IGT to normoglycaemia and elucidating its underlying mechanisms. They suggest that improvements in both insulin resistance and insulin secretion capacity can be durable – perhaps even sustained. Even if remission may happen without permanent weight loss, weight loss remains a central determinant in the remission of prediabetes and T2D.

The present results are derived from secondary analyses of the original DPS. The study offers several methodological strengths and novel insights compared with earlier investigations on prediabetes remission, including extended follow-up and combined with systematic monitoring of physical activity, diet, and biochemical measures with repeated assessment of insulin sensitivity and secretion indices. Importantly, all DPS study participants were included in the analyses. Notably, a recent *meta*-analysis [7] examining remission rates following five years of lifestyle interventions included fewer study participants than our current study did. Our findings suggest that initiating lifestyle intervention early during the prediabetic phase of hyperglycaemia to improve dietary quality and physical activity to achieve moderate weight loss can not only prevent the progression to T2D but also normalise glucose tolerance in people with IGT. This approach should be considered as a key public health strategy to combat the global epidemic of T2D. As for limitations, baseline data on insulin sensitivity and secretion were not available for all participants, as 30-min glucose and insulin samples during the OGTT were collected at the beginning of 1996, when the study was already underway. During the follow-up period, individuals who developed T2D were excluded from further monitoring, partly explaining the gradual decrease in the number of participants over time. However, the actual dropout rate in the DPS was below 10% [2,3,12].

To conclude, based on the long follow-up period of the DPS participants with IGT, we found that 32% achieved normoglycaemia at least once, and 11% attained sustained long-term normalisation of glucose metabolism. Although this improvement can be mainly attributed to weight loss, a novel finding in our study is that diet quality and physical activity level – the key determinants of weight change in people with obesity – also independently contribute to the reversal of impaired glucose metabolism during the first 3 years. In addition to improved insulin sensitivity, our results confirm that recovery of insulin secretion capacity plays an essential role in the long-term normalisation of glucose metabolism. These findings underscore that progression from IGT to T2D in people with overweight or obesity is not inevitable but can be altered through long-term lifestyle management. Remission of IGT also significantly reduced the probability of progression to T2D. In people with IGT, long-term weight management, supported by healthier dietary choices and regular physical activity, is an effective strategy for achieving durable remission of hyperglycaemia and preventing the development of T2D.

CRediT authorship contribution statement

Matti Uusitupa: Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization, Formal analysis. **Mikko Valtanen:** Writing – original draft, Formal analysis, Data curation. **Jaana Lindström:** Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Jaakko Tuomilehto:** Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JT owns stocks in Orion Pharma, Aktivolabs, Digostics, and Oriola. MU owns stocks in Orion Pharma. Other authors declare no conflict of interest.

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