Prediabetes remission and cardiovascular morbidity and mortality: post-hoc analyses from the Diabetes Prevention Program Outcome study and the DaQing Diabetes Prevention Outcome study

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Summary

Background Prediabetes is associated with increased risk of cardiovascular disease and heart failure. Multicomponent lifestyle interventions, including diet and physical activity targeting weight loss are recommended for prediabetes management, although their long-term impact on cardiovascular outcomes remains unclear. Reaching prediabetes remission by restoring normal glucose regulation has been shown to profoundly reduce future type 2 diabetes risk outlasting the time of lifestyle intervention. We aimed to investigate whether prediabetes remission is associated with a lower incidence of cardiovascular death or hospitalisation for heart failure compared with non-remission, with a long-term legacy effect.

Methods Post-hoc analyses were performed from two landmark diabetes prevention trials, the US Diabetes Prevention Program Outcomes Study (DPPOS) and the Chinese DaQing Diabetes Prevention Outcomes Study (DaQingDPOS). Remission was assessed using the American Diabetes Association criteria after 1 year (DPPOS) or 6 years (DaQingDPOS) of intervention. The primary endpoint was cardiovascular death or hospitalisation for heart failure over 20 and 30 years, respectively. In DPPOS, inverse probability of treatment weighting adjusted for baseline differences. A unifying meta-analysis was calculated across both data sets for the primary endpoint and all-cause mortality.

Findings For DPPOS, follow-up time is reported from the start of the original Diabetes Prevention Program trial, July 31, 1996, to the end of DPPOS phase 3, Feb 23, 2020. In total, 2402 participants were included in DPPOS and 540 in DaQingDPOS. In DPPOS, 275 (11·5%) of 2402 participants reached remission after 1 year of intervention compared with 2127 (88·5%) of 2402 not reaching remission. In DPPOS, after a median follow-up of 20 years, the event rate for cardiovascular death or hospitalisation of heart failure was 1·74 (95% CI 0·87–3·48) per 1000 person-years in participants who reached remission versus 4·17 (95% CI 3·55–4·89) in those without remission (p=0·013) with a fully adjusted hazard ratio of 0·41 (95% CI 0·20–0·84; p=0·014). Results remained robust after adjustment, were confirmed in DaQingDPOS (primary endpoint: HR 0·49 [95% CI 0·28–0·84]; p=0·010), and were supported by a pooled meta-analysis. Results were stable when analysing the composite endpoint in those reaching remission at least once during follow-up, with a HR of 0·43 (0·29–0·63; p<0·0001).

Interpretation Reaching prediatbetes remission is linked to a decades-long benefit, halving the risk of cardiovascular death or hospitalisation for heart failure in diverse populations. Targeting remission might represent a new approach to cardiovascular prevention.

Funding German Center for Diabetes Research via the German Federal Ministry of Research, Technology and Space; Ministry of Science, Research, and the Arts Baden-Württemberg; Helmholtz Munich; the Helmholtz Young Investigators Groups funding programme; the Cluster of Excellence EXC-2124; and the German Research Foundation (DFG). For DaQIng: Centers for Disease Control and Prevention, WHO, the China-Japan Friendship Hospital, and Da Qing First Hospital and Fuwai Hospital, Chinese Academy of Medical Sciences. For DPPOS: National Institute of Diabetes and Digestive and Kidney Diseases.

Introduction

Prediabetes is associated with atherosclerotic cardiovascular disease, heart failure, and premature death.[1,2] Insulin resistance, a hallmark of prediabetes, is associated with adverse cardiovascular outcomes even in the absence of prediabetic hyperglycaemia. Prediabetes is defined using different glycaemic thresholds by the American Diabetes Association (ADA), WHO, and

Lancet Diabetes Endocrinol 2025

Published Online December 12, 2025 https://doi.org/10.1016/S2213-8587(25)00295-5

See Online/Comment https://doi.org/10.1016/S2213-8587(25)00360-2

See Online/Comment https://doi.org/10.1016/S2213-8587(25)00366-3

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For the German translation of the abstract see Online for appendix 1

For the Chinese translation of the abstract see Online for appendix 2

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See Online for appendix 3

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published in English from database inception to June 23, 2025. We used the search terms "prediabetes" AND "remission" AND "intervention". Recent meta-analyses involving over 16 000 participants show that multicomponent lifestyle intervention programmes for people with prediabetes effectively lower the risk of type 2 diabetes but have not consistently reduced cardiovascular complications. These multimodal programmes typically focus on weight loss and physical activity rather than specific glycaemic targets. Emerging evidence indicates that remission from prediabetes to normoglycaemia might offer additional preventive benefits, but its impact on cardiovascular events and mortality remains unclear.

Added value of this study

To the best of our knowledge, this is the first analysis to combine data from two independent, large-scale, multicentre clinical intervention trials in the USA and China to examine whether remission from prediabetes to normal glucose regulation is associated with a reduction in the risk of a composite outcome of cardiovascular death or hospitalisation for heart failure. Across both cohorts, remission to normoglycaemia—compared with no remission—was strongly associated with a lower risk of this composite endpoint. These associations remained robust after adjusting for baseline differences, including cardiovascular risk, using inverse probability of treatment weighting in sensitivity analyses.

Implications of all the available evidence

For individuals with prediabetes, treatment goals should prioritise achieving remission from hyperglycaemia to normoglycaemia alongside promoting weight loss. This dual approach appears to offer additional protection against cardiovascular events and mortality. Conceptually, achieving normoglycaemia parallels established strategies in other cardiovascular risk conditions—such as normalising blood pressure in hypertension or lowering elevated cholesterol in hypercholesterolemia—to prevent cardiovascular events and death.

International Diabetes Federation (IDF), who prefer the term intermediate hyperglycaemia (appendix 3 p 1).[2–4] Preventing diabetes in people with prediabetes requires a multidisciplinary approach, including the promotion of a healthy diet and increased physical activity. These lifestyle interventions have been shown to be effective in reducing incident type 2 diabetes and improving cardiovascular risk factors such as hypertension and dyslipidaemia.[5–12] Additionally, lifestyle interventions have been shown to be cost-effective ways to prevent type 2 diabetes.[13] However, major professional diabetes associations, although recommending structured multidisciplinary prevention programmes, do not recommend achieving specific plasma glucose targets as a goal of prevention.[3,14–16]

The DaQing Diabetes Prevention Outcomes study (DaQingDPOS) began in 1986 in Daqing, China, and found that 6 years of structured lifestyle intervention (diet, exercise, or both) in individuals with prediabetes was associated with reductions in cardiovascular mortality by 33% and all-cause mortality by 26% over three decades of follow-up, with the magnitude of benefit closely related to the duration of time spent free from type 2 diabetes.[17–19] By contrast, the Diabetes Prevention Program Outcomes study (DPPOS), the long-term follow-up of the Diabetes Prevention Program (DPP) cohort in the USA that evaluated the long-term effects of the original DPP interventions on diabetes incidence and its complications—which, per protocol, targeted more than 7% weight loss and 150 minutes per week or more of moderate-intensity physical activity during its active phase—did not observe statistically significant reductions in major adverse cardiovascular events (MACE) or mortality after 21 years when analysed according to original randomisation groups.[20] The Finnish Diabetes Prevention study (DPS) yielded comparable findings after 10 years of follow-up.[21] Furthermore, meta-analyses of randomised controlled trials have not shown superiority of lifestyle intervention over standard care in lowering cardiovascular or all-cause mortality among individuals with prediabetes.[22] In light of these observations, the ADA Standards of Care concluded that the long-term impact of lifestyle intervention in people with prediabetes on clinically meaningful microvascular and macrovascular events has not been established.[3]

A potentially transformative strategy in diabetes prevention is the achievement of prediabetes remission—restoration of normal glucose regulation as a therapeutic goal for individuals with prediabetes.[2,23–26] In the current study and in our previous analyses, we defined remission as fasting plasma glucose (FPG) less than 100 mg/dL (<5·6 mmol/L), 2-h plasma glucose less than 140 mg/dL (<7·8 mmol/L), and HbA_{1c} less than 5·7% (39 mmol/mol).[23,25] Although current concepts in prediabetes focus on halting progression to diabetes, the idea that the risk profile can be improved represents a new, more optimistic (albeit more aggressive) goal, and is the basis of the prediabetes remission concept.[2,25] Recent analyses from the DPPOS repository found that reaching remission after 1 year of lifestyle intervention, in addition to meeting guideline-recommended weight loss targets, reduced the incidence of type 2 diabetes more effectively than weight loss alone, with a sustained legacy effect of 6 years.[27] In the Prediabetes Lifestyle Intervention study (PLIS)—despite comparable weight and total fat mass loss—remission was associated with

improved insulin sensitivity, beta-cell function, reduced visceral adiposity and greater protection against type 2 diabetes onset compared with non-remission.[23,28] Taken together, these findings support remission to normal glucose regulation as a clear, measurable, and clinically meaningful endpoint in prediabetes management. Multiple strategies, including structured lifestyle intervention, could be employed to reach this goal, with the potential to redefine prevention beyond weight loss alone.[2]

Heart failure and cardiovascular disease are closely linked to insulin resistance and excess visceral adiposity.[29] Building on the evidence from PLIS demonstrating that remission from prediabetes to normal glucose regulation improves both insulin sensitivity and visceral fat distribution despite similar weight loss,[23] we hypothesised that reaching remission is associated with a lower incidence of the widely used composite endpoint of cardiovascular death or hospitalisation for heart failure compared with non-remission, with a durable legacy effect persisting over decades. To test this hypothesis, we aimed to first examine data from the DPPOS, assessing remission after 1 year of intervention in US participants with prediabetes and tracking outcomes over more than 20 years. We then sought external validation in DaQingDPOS, a more than 30-year follow-up of individuals with prediabetes in Daqing, China. In both cohorts, we also evaluated additional cardiovascular endpoints and all-cause mortality.

Methods

Study design

An observational post-hoc analysis was done using data from two large landmark clinical prevention trials, the DPPOS (USA) and DaQingDPOS (China). We first defined prediabetes and normal glucose regulation using the ADA criteria (FPG <100 mg/dL [<5·6 mmol/L], 2-h plasma glucose <140 mg/dL [<7·8 mmol/L], and HbA_{1c} <5·7% [39 mmol/mol]; appendix 3 p 1). Remission of prediabetes was analysed 1 year after the start of the intervention in DPPOS. As sensitivity analyses, prediabetes remission was analysed after 6 years of lifestyle intervention in DaQingDPOS, and inverse probability of treatment weights was calculated in DPPOS to determine whether potential confounding due to baseline differences, including baseline cardiovascular risk, between people reaching remission and those not reaching remission changes conclusions about the associations of remission to normal glucose regulation with cardiovascular disease outcomes. A unifying meta-analysis was calculated across both data sets for the primary endpoint and all-cause mortality.

In DPPOS, our primary endpoint was the composite event of cardiovascular death or hospitalisation for heart failure. Extended MACE (including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary or peripheral revascularisation, hospitalisation for heart failure or unstable angina, new diagnosis of coronary heart disease, or silent myocardial infarction) was also evaluated as a secondary endpoint. Other secondary endpoints that we evaluated were cardiovascular death, hospitalisation for heart failure, MACE (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular death), and all-cause mortality. We also analysed if reaching remission at least once during follow-up was associated with long-term cardiovascular outcomes in DPPOS.

Our primary endpoint in DaQingDPOS was a composite of cardiovascular death or hospitalisation for heart failure. Other secondary endpoints analysed were cardiovascular death, hospitalisation for heart failure, and MACE (defined in DaQingDPOS as fatal and non-fatal myocardial infarction, stroke, sudden death and hospitalised heart failure, or all-cause mortality), as well as all-cause mortality.

For sensitivity analysis, we also used the WHO/IDF definitions of intermediate hyperglycaemia (FPG 110–125 mg/dL [6·1–6·9 mmol/L] and 2-h plasma glucose 140–199 mg/dL [7·8–11·0 mmol/L]; appendix 3 p 1) in both data sets for all outcomes.

DPPOS study design and participants

The DPPOS is the long-term follow-up of the US Diabetes Prevention Program (DPP) trial. The original DPP enrolled adults (aged ≥25 years) with prediabetes in 23 hospital clinical centres across the USA starting in July, 1996 and ending in August, 2001. The DPP trial compared the effects of an intensive lifestyle intervention (16 sessions delivered by case managers on a one-to-one basis with the aim of reducing weight by 7% and increasing exercise time to 150 min per week), metformin (850 mg twice a day as tolerated), or placebo on the prevention or delay of type 2 diabetes in participants with a BMI of 24 kg/m² or greater (≥22 kg/m² if Asian) and with prediabetes defined by impaired glucose tolerance (IGT) and impaired fasting glucose, according to ADA criteria.[5] The aim of the intensive lifestyle intervention during DPP was a weight reduction of at least 7% of initial body weight and at least 150 min per week of moderate intensity physical activity. Placebo and metformin tables were masked to participants and investigators. The intervention phase, during which participants received the treatment to which they were randomly assigned, lasted an average of 2·8 years before transitioning to the DPPOS follow-up. The DPPOS began in 2002 and enrolled participants regardless of their diabetes status after drug unmasking and results' release. Individuals with early cardiovascular events (ie, within 6 months from screening) were excluded. A detailed description of the methods is given in appendix 3 (pp 21–24) and elsewhere.[20] The trial was registered with ClinicalTrials.gov (NCT00038727). This analysis of prespecified endpoints of DPPOS phase 3, designed to evaluate the long-term effects of the original DPP

interventions on total cancer and MACE, includes participants from the DPP repository randomly assigned to intensive lifestyle intervention, metformin, or placebo and was done using data collected during DPP and during phases 1, 2, and 3 of DPPOS. Adjudication of fatal and non-fatal cardiovascular events was done by a committee of physicians as outlined in appendix 3 (p 21). Follow-up time includes the median 3 years of DPP and up to 23 years during DPPOS (appendix 3 p 2).

DaQingDPOS study design and participants

A detailed description of the methods is given in appendix 3 (p 24). In brief, the objective of the DaQingDPOS was to determine whether people with prediabetes benefit from lifestyle interventions including diet modification and an increase in exercise to delay the development of type 2 diabetes and reduce the overall incidence of diabetic complications.[7,17,19]

In 1986, 576 people aged 25–74 years with impaired glucose tolerance were recruited from 33 community clinics in DaQing, Heilongjiang Province, China. People with previous cardiovascular or cerebrovascular disease were excluded. Participants were randomly assigned to one of three interventions—diet, exercise, or diet plus exercise—or to the control group receiving no specific lifestyle programme. Intensive lifestyle interventions were conducted for 6 years until 1992, with regular counselling and follow-up of more than 30 years. Two physicians, unaware of participants' trial assignments, independently adjudicated outcomes, with disagreements resolved by a third senior physician. Primary cardiovascular events and causes of death were determined from standardised questionnaires, clinical examinations, review of medical records and death certificates. For each outcome, onset was taken as its earliest date of recognition from medical records, interview, or the 20-year and 30-year follow-up examinations.

Statistical analysis

Descriptive statistics for participants were calculated at baseline and at 1 year after randomisation in DPPOS or at the end of lifestyle intervention (6 years) in DaQingDPOS. Categorical variables were summarised using frequency distributions. Continuous variables were summarised using median (IQR) and compared using Wilcoxon tests. Chi-squared tests were used to compare proportions of responders and non-responders who experienced the different outcomes. Crude incidence rates per 1000 person-years of type 2 diabetes for all outcomes were calculated using the number of incident cases and person-years of follow-up. Incident composite primary endpoint, its individual components, and extended MACE in different groups were visualised using Kaplan–Meier curves. Cox proportional hazards models were used to compare the risk of all outcomes between remission and non-remission. In DPPOS,

	Baseline			1 year		
	Remission (n=275)	Non-remission (n=2127)	p value*	Remission (n=275)	Non-remission (n=2127)	p value*
Age (years)	46·9 (41·1–53·4)	50·4 (43·8–57·9)	<0·0001	47·9 (42·1 to 54·4)	51·5 (44·9 to 58·9)	<0·0001
BMI (kg/m²)	32·3 (28·6–37·0)	32·5 (28·8–37·2)	0·828	30·0 (26·5 to 34·2)	31·4 (27·7 to 36·2)	0·025
Change in BMI (kg/m²)	..	..	..	–2·2 (–0·6 to –3·8)	–0·7 (0·3 to –2·1)	<0·0001
Weight (kg)	91·8 (81·1–105·9)	90·5 (79·0–103·7)	0·227	84·2 (75·2 to 97·1)	87·8 (76·1 to 101·3)	<0·001
Fasting glucose (mmol/l)	5·7 (5·5–5·9)	5·8 (5·6–6·2)	<0·0001	5·2 (5·0 to 5·4)	5·7 (5·4 to 6·0)	<0·0001
30 min OGTT glucose (mmol/l)	9·0 (8·3–9·7)	9·3 (8·5–10·3)	<0·0001	8·2 (7·3 to 9·2)	9·3 (8·4 to 10·4)	<0·0001
120 min OGTT glucose (mmol/l)	8·7 (8·1–9·4)	9·0 (8·3–9·9)	<0·0001	6·3 (5·4 to 6·9)	8·5 (7·3 to 9·8)	<0·0001
HbA_{1c} (mmol/mol)	36·6 (34·4–38·8)	41·0 (37·7–43·2)	<0·0001	35·5 (33·3 to 37·7)	41·0 (37·7 to 43·2)	<0·0001
HbA_{1c} (%)	5·5 (5·3–5·7)	5·9 (5·6–6·1)	<0·0001	5·4 (5·2 to 5·6)	5·9 (5·6 to 6·1)	<0·0001
Fasting insulin (pmol/l)	132·0 (96·0–186·0)	138·0 (96·0–198·0)	0·222	96·0 (60·0 to 144·0)	120·0 (84·0 to 180·0)	<0·0001
30 min OGTT insulin (pmol/l)	528·0 (342·0–792·0)	516·0 (360·0–732·0)	0·671	468·0 (312·0 to 678·0)	498·0 (336·0 to 702·0)	0·052
LDL cholesterol (mmol/l)	3·1 (2·6–3·7)	3·2 (2·6–3·7)	0·510	3·0 (2·4 to 3·6)	3·1 (2·6 to 3·7)	0·0120
uACR (mg/g)	5·0 (3·7–9·3)	5·4 (3·7–9·5)	0·273	..	..	..
eGFR (mL/min/1·73 m²)	104·8 (90·9–112·0)	102·3 (89·5–110·9)	0·076	105·2 (95·4 to 111·5)	99·8 (88·3 to 109·0)	<0·0001
CRP (mg/dL)	0·3 (0·1–0·6)	0·4 (0·2–0·7)	0·006	0·2 (0·1 to 0·4)	0·3 (0·1 to 0·7)	<0·0001
NT-proBNP	32·5 (17·5–65·3)	36·5 (19·3–65·1)	0·4004	..	..	..

Data are median (IQR) unless indicated otherwise. eGFR was calculated using the 2021 chronic kidney disease epidemiology collaboration equation from age, sex, and serum creatinine concentrations. ACR was missing at baseline for ten responders and for 24 non-responders. CRP was missing at baseline for three non-responders and at year 1 for one non-responder. NT-proBNP was measured at baseline visits in 1957 of the 2402 participants included in this study, 225 responders, and 1732 non-responders. uACR=urinary albumin to creatinine ratio. ADA=American Diabetes Association. CRP=C-reactive protein. DPPOS=Diabetes Prevention Program Outcomes Study. eGFR=estimated glomerular filtration rate. OGTT=oral glucose tolerance test. NT-proBNP=N-terminal pro-B-type natriuretic peptide. *p values were derived from Wilcoxon tests.

Table 1: **DPPOS: descriptive characteristics of DPP participants according to remission or non-remission (ADA criteria) at baseline and at year 1 after randomisation**

follow-up time for these events for each participant was calculated starting at year 1 when remission or non-remission was assessed. In DaQingDPOS, follow-up time was calculated starting at year 6 when remission or non-remission was assessed. For all outcomes in DPPOS, we fit Cox proportional hazards models that were adjusted for age, sex, race or ethnicity, treatment assignment, baseline weight, baseline smoking status, baseline use of blood pressure lowering and lipid lowering medication. A second model was further adjusted for time-dependent diabetes. To further adjust for potential baseline confounders, we conducted a sensitivity analysis using Inverse Probability of Treatment Weights, which was calculated as described in appendix 3 (p 23). For all outcomes in DaQingDPOS, we fit Cox proportional hazards models that adjusted for age, sex, baseline smoking status, baseline BMI, baseline systolic blood pressure, baseline cholesterol, intervention group, change of body weight at the end of year 6, and use of insulin or oral glucose-lowering agents, blood pressure-lowering medication, and lipid-lowering agents during the follow-up period. A second model was further adjusted for time-dependent diabetes.

For analysing if reaching remission at least once during follow-up was associated with long-term cardiovascular outcomes in DPPOS, Cox proportional hazards models were fitted for each outcome, adjusting for baseline age, sex, race or ethnicity, treatment assignment, baseline weight, smoking status, use of antihypertensive medication, and use of statins. To account for the cessation of remission assessments after diabetes onset, models additionally included an indicator for diabetes development during follow-up and the time spent with diabetes (calculated as time-to-outcome minus time-to-diabetes diagnosis).

We also evaluated whether different FPG thresholds after 1 year of intervention in DPPOS could serve as a proxy for prediabetes remission and predict long-term cardiovascular benefit. HR for the composite endpoint of cardiovascular death or hospitalisation for heart failure, and for extended MACE, were calculated for multiple FPG cut-offs, with error bars representing 95% CIs.

	Cases/person-years	Event rate/1000 person-year (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)
Cardiovascular death or hospital for heart failure					
Non-remission	147/35289	4·17 (3·55–4·89)	Ref	Ref	Ref
Remission	8/4600	1·74 (0·87–3·48)	0·41 (0·20–0·84)	0·47 (0·23–0·97)	0·50 (0·24–1·00)
p value	..	0·013	0·014	0·041	0·050
Hospital for heart failure					
Non-remission	71/35 100	2·02 (1·60–2·55)	Ref	Ref	Ref
Remission	1/4590	0·22 (0·03–1·55)	0·11 (0·02–0·76)	0·12 (0·02–0·90)	0·15 (0·02–1·08)
p value	..	0·007	0·025	0·039	0·059
Cardiovascular death					
Non-remission	93/35 531	2·62 (2·14–3·21)	Ref	Ref	Ref
Remission	7/4601	1·52 (0·73–3·19)	0·56 (0·27–1·24)	0·70 (0·32–1·53)	0·70 (0·32–1·55)
p value	..	0·161	0·158	0·369	0·382
Extended MACE					
Non-remission	333/33 454	9·95 (8·95–11·08)	Ref	Ref	Ref
Remission	28/4494	6·23 (4·31–9·01)	0·63 (0·43–0·93)	0·70 (0·47–1·04)	0·68 (0·46–1·02)
p value	..	0·016	0·020	0·078	0·060
MACE					
Non-remission	209/34 665	6·03 (5·27–6·90)	Ref	Ref	Ref
Remission	19/4494	4·23 (2·70–6·62)	0·70 (0·44–1·12)	0·81 (0·50–1·31)	0·77 (0·47–1·25)
p value	..	0·137	0·132	0·383	0·291
Mortality					
No-remission	331/36 047	9·18 (8·25–10·22)	Ref	Ref	Ref
Remission	28/4630	6·05 (4·18–8·75)	0·65 (0·44–0·96)	0·78 (0·53–1·16)	0·76 (0·51–1·14)
p value	..	0·033	0·030	0·226	0·187

MACE included non-fatal heart attack, non-fatal stroke, or cardiovascular death. Extended MACE included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary or peripheral revascularisation, hospitalisation for heart failure or unstable angina, new diagnosis of coronary heart disease, or silent myocardial infarction. ADA=American Diabetes Association. DPPOS=Diabetes Prevention Program Outcomes Study. HR=hazard ratio. MACE=major adverse cardiovascular event. *HR adjusted for sex, race and ethnicity, treatment assignment, baseline age, baseline weight, baseline smoking status, baseline use of blood pressure lowering and lipid lowering medication.[1] †HR further adjusting for time dependent diabetes which developed after the 1-year intervention phase (time dependent variable).

Table 2: **DPPOS: HRs of indicated endpoints comparing prediabetes remission to normal glucose regulation (after 1 year of lifestyle intervention) compared with non-remission (defined by ADA criteria) after more than 20 years of follow-up on composite endpoint of cardiovascular death and hospitalisation for heart failure and other cardiovascular outcomes**

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.

Results

We first established the relationship between prediabetes remission and cardiovascular morbidity and mortality in DPPOS.[20,30] 2402 (74%) of the original 3234 DPP participants were included in the current analysis. Reasons for exclusion of participants are given in the consort flow chart (appendix 3 p 25).

Table 1 shows anthropometric and metabolic baseline characteristics in DPPOS stratified by response. Similar to previous studies, individuals reaching remission were younger and had lower glucose levels at baseline than individuals not in remission, median 5·7 mmol/l (IQR 5·5–5·9) versus 5·8 mmol/l (5·6–6·2), p<0·0001 (table 1).[23,24,27,28] In total, 93 (34%) of 275 participants reaching remission after 1 year of intervention were diagnosed with type 2 diabetes by the end of DPPOS observation phase (phase 3) compared with 1209 (57%) of 2127 not reaching remission (p<0·0001; appendix 3 p 2). People reaching remission had lower type 2 diabetes incidence (2·36 cases per 100 person-years) than those not reaching remission (5·41 cases per 100 person-years, p<0·0001). Follow-up for type 2 diabetes development was higher in people who reached remission (median 15·0 years [IQR 8·0–21·5]), compared with people who had not (median 8·2 years [3·5–19·0]; appendix 3 p 2). To account for the different type 2 diabetes risks of the two groups due to different glycaemia and thus potential cardiovascular impairment imposed by type 2 diabetes, the cardiovascular outcome analysis was also adjusted for time-dependent type 2 diabetes, defined based on development of type 2 diabetes during follow-up for specific cardiovascular outcomes.

In DPPOS, the median follow-up times for the composite endpoint of cardiovascular death or hospitalisation for heart failure were comparable between groups with 20·3 years (IQR 13·5–21·0) in people reaching remission and 20·0 years (13·7–21·0) in people not reaching remission (appendix 3 p 2). The event rate of the primary endpoint, cardiovascular death or hospitalisation for heart failure was 1·74 (95% CI 0·87–3·48) per 1000 person-years in people reaching remission and 4·17 (95% CI 3·55–4·89) per 1000 person-years in people not reaching remission after 1 year of intervention (p=0·014). The crude and the fully adjusted hazard ratios (HR) comparing people reaching prediabetes remission to those not reaching remission were 0·41 (95% CI 0·20–0·84; p=0·014) versus 0·47 (95% CI 0·23–0·97; p=0·041; table 2). Figures 1A–C show the Kaplan–Meier curves for the composite endpoint of cardiovascular death or hospitalisation for heart failure, as well as its single components. Raw and adjusted HRs for individual endpoints are given in table 2. We additionally included a composite outcome of more cardiovascular endpoints into the analysis, extended MACE, with an event rate of 6·23 (95% CI 4·31–9·01) per 1000 person-years in people reaching remission and 9·95 (95% CI 8·95–11·08) per 1000 person-years in people not reaching remission (p=0·016). The crude HR for extended MACE comparing people reaching prediabetes remission to those not reaching remission was 0·63 (95% CI 0·43–0·93; p=0·020) while the adjusted HR was 0·70 (95% CI 0·47–1·04; p=0·078; table 2, figure 1D). The event rate of mortality was 6·05 (95% CI 4·18–8·75) per 1000 person-years in people reaching remission and 9·18 (8·25–10·22) per 1000 person-years in people not reaching remission (p=0·033). The crude HR for mortality comparing people who reached prediabetes remission to those not reaching remission was 0·65 (95% CI 0·44–0·96; p=0·030) and the adjusted HR was 0·78 (0·53–1·16; p=0·226). As sensitivity analysis, we performed the same analysis using the WHO/IDF definition of normal glucose regulation. The analysis showed comparable results to the analysis using the ADA definition (appendix 3 pp 5, 17). For the sensitivity

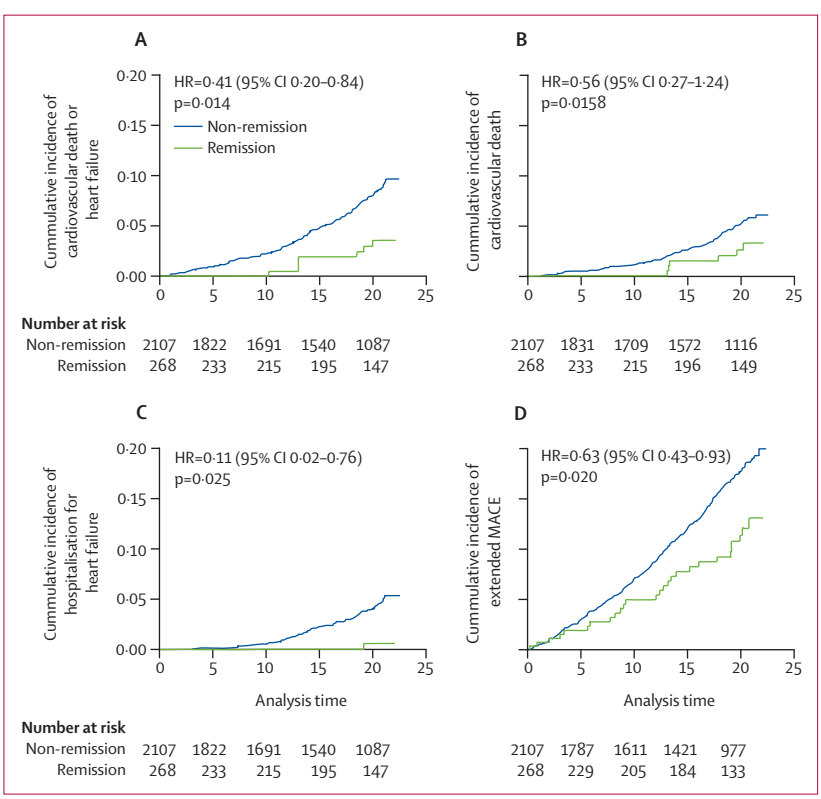

Figure 1: **DPPOS: Kaplan–Meier curves for risk of composite endpoint cardiovascular death or hospitalisation for heart failure (A), cardiovascular death (B), hospitalisation for heart failure (C), and extended MACE (D) by remission status after 1 year of lifestyle intervention and over up to 20 years of follow-up**
Remission status was determined according to ADA criteria. Extended MACE included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary or peripheral revascularisation, hospitalisation for heart failure or unstable angina, new diagnosis of coronary heart disease, or silent myocardial infarction. DPPOS=Diabetes Prevention Program Outcomes Study. MACE=major adverse cardiovascular event.

analysis where we balanced baseline differences using stabilised inverse probability of treatment weights, the composite primary endpoint remained reduced after using inverse probability of treatment weights for baseline differences with a crude HR of 0·38 (95% CI 0·16–0·88; p=0·024); reduction in risk of the other cardiovascular disease outcomes was also present (appendix 3 pp 7, 18, 26).

	Baseline			6 years		
	Remission (n=72)	Non-remission (n=468)	p value	Remission (n=72)	Non-remission (n=468)	p value
Age (years)	43·0 (38·5–51·5)	45·0 (38·0–51·0)	0·743	49·0 (44·5 to 57·5)	51·0 (44·0 to 57·0)	0·743
Sex (male n%)	46 (63·9%)	252 (53·8%)	0·111	46 (63·9%)	252 (53·8%)	0·111
Smoking (n%)	33 (45·8%)	186 (39·7%)	0·327	..	..	..
BMI (kg/m²)	24·8 (21·1–28·0)	26·3 (23·5–28·4)	0·017	24·9 (21·6 to 26·5)	25·5 (23·0 to 27·6)	0·011
BMI change (kg/m²)	..	..	..	–0·39 (–1·54 to 1·45)	–0·72 (–1·83 to 0·32)	0·180
Systolic blood pressure (mmHg)	122·0 (110·0–140·0)	130·0 (120·0–150·0)	0·118	120·0 (112·0 to 140·0)	130·0 (120·0 to 140·0)	0·014
Diastolic blood pressure (mmHg)	88·5 (80·0–97·5)	88·0 (80·0–96·0)	0·913	80·0 (70·0 to 90·0)	85·0 (80·0 to 90·0)	0·079
Fasting plasma glucose (mmol/L)	5·2 (4·6–5·6)	5·6 (5·1–6·2)	<0·001	5·1 (4·6 to 5·4)	6·6 (5·8 to 8·4)	<0·0001
2h-PG (mmol/L)	8·6 (8·1–9·1)	8·9 (8·3–9·7)	0·004	6·3 (5·3 to 7·0)	11·8 (9·1 to 14·0)	<0·0001
Fasting insulin (mU/L)	16·5 (10·0–26·0)	21·0 (14·0–31·0)	0·008	..	..	..
Triglycerides (mmol/L)	1·1 (0·9–1·6)	1·6 (0·9–2·3)	0·023	1·1 (0·9 to 1·9)	1·6 (1·1 to 2·5)	<0·0001
Total cholesterol (mmol/L)	4·8 (4·1–5·6)	4·9 (4·4–5·7)	0·640	4·7 (4·2 to 5·2)	5·2 (4·5 to 5·7)	0·310

Continuous data are presented as median (IQR), categorical data are presented as n (%), fasting insulin is shown with 95% CI. 2h-PG=2-hour plasma glucose after 75-g oral glucose tolerance test. ADA=American Diabetes Association. DaQingDPOS=DaQing Diabetes Prevention Outcomes Study.

Table 3: **DaQingDPOS: descriptive characteristics of DaQingDPOS participants according to remission or non-remission (ADA criteria) at baseline and at end of lifestyle intervention (6 years)**

	Cases/person-years	Event rate/1000 person-year (95% CI)	Crude HR (95% CI)	Adjusted HR* (95% CI)	Adjusted HR† (95% CI)
Cardiovascular death or hospitalised heart failure					
Non-remission	160/9393	17·0 (14·6–19·9)	Ref	Ref	Ref
Remission	15/1579	9·5 (5·7–15·8)	0·53 (0·31–0·90)	0·45 (0·26–0·78)	0·49 (0·28–0·84)
p value	..	..	0·019	0·005	0·010
Hospitalised heart failure					
Non-remission	74/9379	7·9 (6·3–9·9)	Ref	Ref	Ref
Remission	6/1584	3·8 (1·7–8·4)	0·44 (0·19–1·00)	0·38 (0·16–0·91)	0·39 (0·16–0·93)
p value	..	..	0·050	0·029	0·034
Cardiovascular death					
Non-remission	131/9522	13·8 (11·6–16·3)	Ref	Ref	Ref
Remission	13/1585	8·2 (4·8–14·1)	0·58 (0·33–1·03)	0·51 (0·28–0·91)	0·56 (0·31–1·02)
p value	..	..	0·062	0·024	0·059
MACE					
Non-remission	347/7566	45·9 (41·3–51·0)	Ref	Ref	Ref
Remission	37/1370	27·0 (19·6–37·3)	0·56 (0·40–0·78)	0·54 (0·38–0·77)	0·61 (0·43–0·87)
p value	..	..	0·004	0·001	0·006
Mortality					
Non-remission	255/9522	26·8 (23·7–30·3)	Ref	Ref	Ref
Remission	26/1585	16·4 (11·2–24·1)	0·59 (0·40–0·89)	0·48 (0·31–0·72)	0·55 (0·36–0·84)
p value	..	..	0·011	<0·001	0·006

Cardiovascular death or hospitalised heart failure included fatal myocardial infarction, stroke, sudden death, or hospitalised heart failure. Cardiovascular death included fatal myocardial infarction, stroke and sudden death. MACE included fatal and non-fatal myocardial infarction, stroke, sudden death and hospitalised heart failure, or all-cause death. DaQingDPOS=DaQing Diabetes Prevention Outcomes Study. ADA=American Diabetes Association. HR=hazard ratio. MACE=major adverse cardiovascular event. *HR adjusted for age, sex, baseline smoking, baseline BMI, baseline systolic blood pressure, baseline cholesterol, intervention, use of medications (including insulin plus oral glucose lowering mediation, blood pressure lowering mediation, and lipid lowering agents), and change of body weight at the end of year 6. †HR, further adjusting for diabetes which developed after completion of 6-year intervention trial (as time-dependent variable).

Table 4: **DaQingDPOS: HRs of prediabetes remission to normal glucose regulation (end of lifestyle intervention) compared with non-remission (defined by ADA criteria) after more than 30 years of follow up on the composite endpoint of cardiovascular death and heart failure and other cardiovascular outcomes as described**

Finally, we assessed whether reaching remission at least once during follow-up was associated with cardiovascular outcomes. Overall, 875 (36%) of participants reached remission at least once by ADA criteria and 1589 (66%) by WHO criteria. The analysis shows that remission at least once during follow-up was significantly associated with reduced risk for most cardiovascular outcomes, regardless of whether ADA or WHO criteria were applied (appendix 3 pp 9, 10). For example, the HR for the composite event of cardiovascular death or hospitalisation for heart failure comparing participants who reached remission according to ADA criteria at least once during follow-up with participants who did not was 0·43 (95% CI 0·29–0·63; p<0·0001) when adjusted for diabetes development during follow-up.

In DaQingDPOS, among 576 participants with prediabetes, 36 were lost to follow-up as shown in the consort flow chart (appendix 3 p 27). All other participants were analysed. For sensitivity analysis, prediabetes remission was assessed at the end of the 6-year intervention phase in DaQingDPOS. Baseline characteristics of the 540 participants separated into remission and non-remission groups by different classification are given in table 3 (ADA criteria) and appendix 3 pp 12 (WHO criteria).

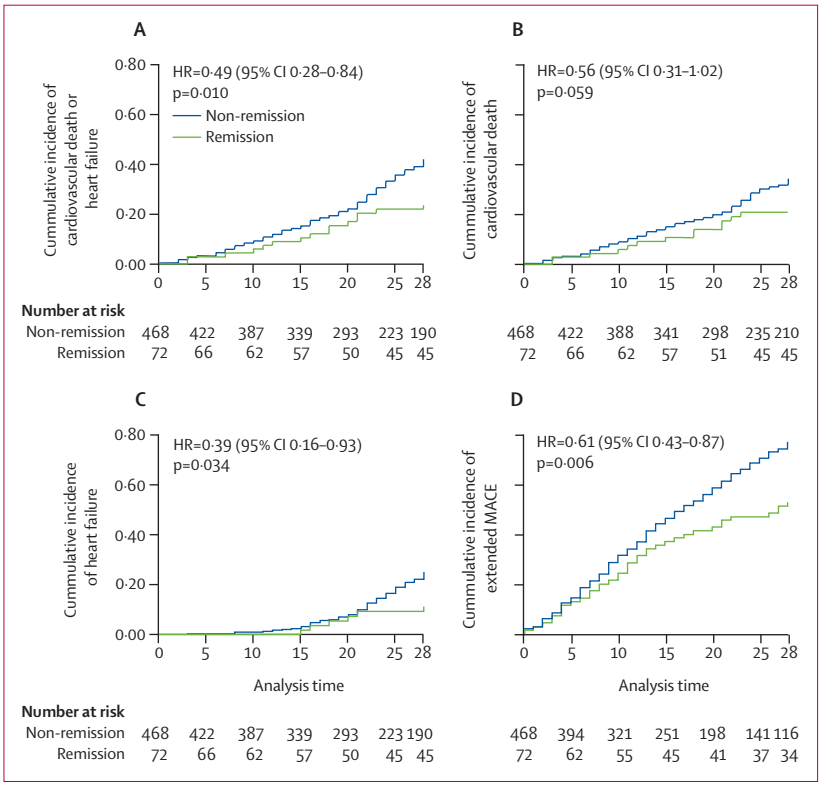

Figure 2: **DaQingDPOS: Kaplan–Meier curves for risk of composite endpoint cardiovascular death or hospitalisation for heart failure (A), cardiovascular death (B), hospitalisation for heart failure (C), and MACE (D) by remission status after 6 years of lifestyle intervention over 30 years of follow-up**
Remission status was determined according to ADA criteria. HRs calculated from Cox proportional hazards analyses adjusted for age, sex, smoking, BMI, systolic blood pressure, cholesterol, intervention, change of bodyweight at the end of year 6, medications, and diabetes which developed after completion of the 6-year intervention trial (as time-dependent variable). MACE included fatal and non-fatal myocardial infarction, stroke, sudden death and hospitalised heart failure, or all-cause death. DaQingDPOS=DaQing Diabetes Prevention Outcomes Study. HR=hazard ratio. MACE=major adverse cardiovascular event.

The median follow-up time of more than 30 years in DaQingDPOS permitted to reliably assess long-term cardiovascular outcomes in this primary prevention setting. The composite event rate of cardiovascular death or hospitalisation for heart failure, hospitalisation of heart failure, cardiovascular death, and MACE (including fatal and non-fatal myocardial infarction, stroke, sudden death, and hospitalised heart failure or all-cause death) was 9·5 (95% CI 5·7–15·8), 3·8 (1·7–8·4), 8·2 (4·8–14·1), and 27·0 (19·6–37·3) per 1000 person-years in people reaching remission and 17·0 (14·6–19·9, p=0·021), 7·9 (6·3–9·9, p=0·067), 13·8 (11·6–16·3, p=0·063), and 45·9 (41·3–51·0, p=0·001) per 1000 person-years in people not reaching remission, respectively (table 4). The crude HR (remission compared with non-remission) was 0·53 (95% CI 0·31–0·90; p=0·019) for the composite endpoint of cardiovascular death or hospitalised heart failure, 0·58 (0·33–1·03; p=0·062) for cardiovascular death, 0·44 (0·19–1·00; p=0·050) for hospitalisation for heart failure, 0·56 (0·40–0·78; p=0·004) for MACE, and 0·59 (95% CI 0·40–0·89; p=0·011) for mortality (table 4). After adjustment for age, sex, BMI, systolic blood pressure, smoking status, cholesterol, intervention, use of medications (insulin or oral glucose lowering agents, blood pressure lowering, and lipid lowering medication), change of body weight at the end of year 6, and the time-dependent diabetes after completion of the 6-year intervention, the HRs between people reaching remission and non-remission were 0·49 (95% CI 0·28–0·84) for cardiovascular death or hospitalisation for heart failure (p=0·010), 0·56 (95% CI 0·31–1·02) for cardiovascular death (p=0·059), 0·39 (95% CI 0·16–0·93) for hospitalisation for heart failure (p=0·034), 0·61 (95% CI 0·43–0·87) for MACE (p=0·006), and 0·55 (95% CI 0·36–0·84) for mortality (p=0·006). HRs of all cardiovascular endpoints stayed significant after adjusting change of bodyweight (table 4). Figure 2 shows the adjusted Kaplan–Meier curves for the cardiovascular endpoints. We also analysed the DaQingDPOS by the WHO glucose threshold for normal glucose regulation for sensitivity analysis and observed comparable results (appendix 3 pp 13, 19).

To understand if the association between prediabetes remission and the composite primary endpoint and all-cause mortality can also be shown in a larger data set with a higher number of incident cases, a pooled meta-analysis of DPPOS and DaQingDPOS was done. The pooled crude HR of cardiovascular death or hospitalisation for heart failure was 0·48 (95% CI 0·31–0·74; p=0·0008; I^2=0·0%), and the pooled adjusted HR was 0·47 (95% CI 0·30–0·72, p=0·0006; I^2=0·0%), when comparing people reaching remission with people not reaching remission by ADA criteria (appendix 3 p 15). The pooled crude HR of all-cause mortality was 0·62

(95% CI 0·47–0·82, p=0·0009; I^2=0·0%), and the pooled adjusted HR was 0·63 (0·47–0·84, p=0·0014; I^2=62%), when comparing people reaching remission with people not reaching remission by ADA criteria (appendix 3 p 15). The results remained robust when the analysis was performed based on WHO criteria (appendix 3 p 15).

The definition of prediabetes remission includes FPG, 2-h plasma glucose, and HbA_{1c} cut-offs, all occurring together. Since these three measures are not readily available in primary care practices worldwide, we next evaluated a potential threshold of FPG as a proxy for remission to normal glucose regulation to predict reduction of cardiovascular outcomes risk. The lowest FPG value associated with a statistically significant risk reduction for both endpoints was 97 mg/dL or less, compared with participants who did not reach this threshold (HR for cardiovascular death or heart failure: 0·63 [95% CI 0·42–0·96], p=0·030; HR for extended MACE: 0·71 [0·55–0·93], p=0·011; appendix 3 pp 16, 20).

Discussion

Our analysis shows that prediabetes remission in two independent landmark randomised, controlled, diabetes prevention trials—including participants from diverse cultural and ancestral backgrounds—was associated with a substantially lower risk of cardiovascular morbidity and mortality. This association emerged during the decades-long follow-up after the active intervention had been concluded, suggesting a strong legacy effect of remission. The relationship remained robust after propensity score matching for baseline differences between individuals who reached remission and those who did not. These findings support the integration of prediabetes remission, alongside established weight loss targets, into the multimodal clinical management for the prevention of type 2 diabetes and cardiovascular morbidity and mortality in individuals with prediabetes.[2,31]

The DPPOS originally reported that neither lifestyle intervention nor metformin reduced MACE over 21 years of follow-up, despite effective prevention of type 2 diabetes.[20] Similarly, the Finnish DPS did not report such an effect.[21] In DPPOS, one explanation was that extensive out-of-study use of lipid lowering and blood pressure lowering pharmacotherapy, and reduction in the use of study metformin, together with out-of-study metformin use over time could have diluted the effects of the interventions. In our analysis, we adjusted for medication use and confirmed our findings in the independent DaQingDPOS after a 6-year lifestyle intervention in China.[7,17,19] Independent results from both studies, together with a pooled meta-analysis, indicate that prediabetes remission—reached after 1 year of intervention in DPPOS or after 6 years in DaQingDPOS—is associated with a legacy effect on cardiovascular outcomes persisting two-to-three decades after the intervention concluded. These associations were consistent whether normal glucose regulation was defined by ADA or WHO criteria, and whether reaching remission at least once during follow-up was assessed and was robust to adjustment for the development of type 2 diabetes.

Our findings are consistent with evidence from both populations with prediabetes and with type 2 diabetes, showing that remission is associated with improved long-term outcomes. In the randomised controlled Look AHEAD trial in people with type 2 diabetes, a post-hoc analysis reported that remission from type 2 diabetes (HbA_{1c} less than 6·5% without glucose-lowering therapy), reached through an intensive lifestyle intervention, was linked to a substantially lower risk of cardiovascular events and chronic kidney disease when analysed in people who were in remission at least once during the study period.[32] In our analysis, being in remission at least once during the follow-up period in DPPOS was linked to a comparable reduction in cardiovascular outcomes. In the observational Kailuan cohort study from China, including over 14 000 people with prediabetes, remission to normoglycaemia was associated with significant reductions in myocardial infarction, stroke, and all-cause mortality, and remained robust after adjustment for multiple cardiovascular risk factors.[33] Together, these findings reinforce the concept that reaching and maintaining normoglycaemia by means of a multimodal lifestyle intervention might confer meaningful cardiometabolic benefit.

It is therefore important to elucidate the mechanisms linking prediabetes remission to incident cardiovascular outcomes. Although weight loss can improve multiple metabolic parameters, our previous findings from the PLIS study indicate that remission is not solely determined by the magnitude of weight reduction.[23,28] Participants who reached remission and those who did not, following a multimodal lifestyle intervention, experienced comparable weight loss (>5% of initial bodyweight) and total body fat loss. However, remission was accompanied by greater improvements in insulin sensitivity, more pronounced reductions in visceral adipose tissue, and lower levels of low-grade inflammation.[23] These observations suggest that remission, although partly overlapping, might capture additional physiological benefits than weight loss alone. Moreover, remission without weight loss[28] or remission without structured intervention[34] is characterised by improved insulin sensitivity, increased insulin secretion,[28,34] and bodyfat re-distribution from visceral to subcutaneous depots.[28] These variables improve more in people reaching remission than those who did not, even with similar weight changes between the groups as shown in our recent analysis from PLIS.[28]

Thus, remission from prediabetes to normoglycaemia might serve as both a biomarker and a therapeutic target, encapsulating a spectrum of favourable cardiometabolic changes.[32,35] In our analysis, remission to normoglycaemia was defined using FPG, 2h-PG, and HbA_{1c} simultaneously.

Recognising that not all of these measures are routinely available in primary care settings worldwide, we examined whether FPG alone—a widely accessible laboratory parameter—could predict remission. Our findings suggest that an FPG of 97 mg/dL (5·3 mmol/L) or lower after 1 year of intervention might be associated with a reduced risk of cardiovascular outcomes decades later. Given its broad availability across high-income, middle-income, and low-income settings, FPG could represent a practical surrogate marker for remission. However, this observation should be considered hypothesis-generating and requires confirmation in prospective, controlled studies before being adopted as a treatment target in clinical practice.

The limitations of this study include the analyses being post hoc, although cardiovascular outcomes were prespecified in both trials. Baseline characteristics differed between individuals who reached remission and those who did not;[23,24,32,36] moreover, remission was more likely among individuals with baseline glycaemic values closer to the threshold for normal glucose regulation than among those nearer the diagnostic threshold for type 2 diabetes, which might also have influenced the results. We addressed this by applying inverse probability of treatment weighting to account for most baseline differences and the associations remained robust. The number of primary endpoint events was limited in both DPPOS and DaQingDPOS, which might have influenced the estimates. To mitigate this, we conducted a meta-analysis across both studies, which strengthened the observed association in a larger event dataset. Large, prospective randomised trials will be required to confirm and extend these findings.

Regardless of baseline glycaemia in people with prediabetes, our data suggests the benefit of remission to normoglycaemia as an additional therapeutic target for prevention of type 2 diabetes and heart disease in people living with prediabetes, although more effort might be needed for people with higher baseline glycaemia. As the rates of remission of prediabetes to normal glucose regulation in DPPOS and DaQingDPOS were rather low at 11·4% and 13·3% of participants respectively, it will be important in the future to determine how people not reaching remission can be amended to remission. Clearly, future studies will need to determine how lifestyle-based remission programmes are prioritised against, or alternatively integrated with, pharmacological or other medical approaches that might play a role in prevention strategy and policy.

Taken together, these post-hoc analyses from two diabetes prevention trials suggest that remission of prediabetes to normal glucose regulation is linked to a lower risk of cardiovascular death or hospitalisation for heart failure, as well as all-cause mortality, in DPPOS and DaQingDPOS. These associations remained robust after comprehensive adjustment for baseline differences using inverse probability of treatment weighting. Prediabetes remission to normal glucose regulation thus emerges as a consistent, measurable, and globally applicable prevention target—one with a long-term benefit—that should be considered in future guidelines, not only for preventing type 2 diabetes but also for the primary prevention of cardiovascular morbidity and mortality in diverse populations worldwide.[25]

Contributors

ALB formulated the primary research question and hypothesis, and drafted the initial analysis plan. ALB, NM, RJvS, and EVA revised the analysis plan; EVA and QG conducted the data analysis supervised by RLH, RJvS (DPPOS) and GL (DaQingDPOS); ALB, EVA, QG, RLH, JW, LS, AS, XQ, SH, MG, SRB, AF, NS, HP, EWG, NM, RJvS, GL, and ALB interpreted the data; ALB wrote the first draft of the manuscript. All authors revised, edited, and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. EVA and GL accessed and verified the data.

Data sharing

DPP and DPPOS data are publicly available through the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Repository. DaQingDPOS datasets are not publicly accessible due to national data protection regulations and ethical restrictions designed to protect participant privacy. They can be requested after publication by contacting the corresponding author. Each request will be reviewed by the respective data steering committees, and approved access will require a formal data use agreement.

Declaration of interests

RJvS was funded by the Funding Programme Helmholtz Young Investigators Groups (project ID number VH-NG-1619) and the Cluster of Excellence EXC-2124 (project number 03.007). LS has received research support for an unrelated research project from Novo Nordisk. RLH was supported by an intramural research program of the National Institutes of Health. NM states that the University Hospital Aachen received contracted fees and travel support from Boehringer Ingelheim and Novo Nordisk, consulting fees from Abbot, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Novo Nordisk and Sanofi Aventis, and contracted payments for lectures from AstraZeneca, Bayer, Boehringer Ingelheim, Lilly, MSD, Novo Nordisk, and Sanofi Aventis. All other authors declare no competing interests.

Acknowledgments

We thank all the participants and their relatives of the respective cohorts and the numerous people who worked on this endeavor and made it possible. Especially we would like to thank the technical and nursing staff for their passionate commitment. Our special thanks go to the late Professor Xiaoren Pan (China–Japan Friendship Hospital, Beijing, China). We thank all investigators that conceived and executed DPP and DaQingDPS. The DPP was conducted by the DPP Research Group and supported by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the General Clinical Research Center Program (GCRC), the National Institute of Child Health and Human Development (NICHD), the National Institute on Aging (NIA), the Office of Research on Women's Health (ORWH), the Office of Research on Minority Health (ORMH), the Centers for Disease Control and Prevention (CDC), and the American Diabetes Association (ADA). The resources from the DPP were supplied by NIDDK Central Repository (NIDDK-CR). This manuscript was not prepared under the auspices of the DPP Research Group and does not represent analyses or conclusions of the DPP Research Group, the CDC, NIDDK-CR, or NIH. The contributions of the NIH authors were made as part of their official duties as NIH federal employees, are in compliance with agency policy requirements, and are considered Works of the United States Government. However, the findings and conclusions presented in this paper are those of the authors and do not necessarily reflect the views of the NIH of the US Department of Health and Human Services. The DPPOS and the DaQingDPOS were supported from 1986 to 1992 by the Ministry of Public Health of the People's Republic of China, and Da Qing First Hospital; from 2004 to 2009 by the US CDC–WHO Cooperative

Agreement (U58/CCU424123–01–02), China–Japan Friendship Hospital, and DaQing First Hospital; and from 2015 to 2018 by the US CDC–Chinese Center for Disease Control and Prevention Cooperative Agreement (5U19GH000636–05); and funded by the Chronic Diseases National Science and Technology Major Project (2024ZD0531500; 2024ZD0531505), and the Fuwai Hospital, Chinese Academy of Medical Sciences, High Level Hospital Clinical Research Funding (grant number: 2024-GSP-GG-5 and 2025-GSP-GG-6). This work was funded by the German Center for Diabetes Research via the German Federal Ministry of Research, Technology and Space (01GI0925); Ministry of Science, Research, and the Arts Baden-Württemberg; Helmholtz Munich; the Helmholtz Young Investigators Groups funding programme to RJvS (project ID number VH-NG-1619); the Cluster of Excellence EXC-2124 (project number 03.007); and a grant from the German Research Foundation (DFG) to ALB (GRK2816).

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