

# THE LANCET

## Diabetes & Endocrinology

### **Supplementary appendix 3**

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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## Supplementary Appendix

### **Prediabetes Remission and Cardiovascular Morbidity and Mortality: A post-hoc analysis from Diabetes Prevention Program Outcome Study and the DaQing Diabetes Prevention Outcome Study**

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## Supplementary Data Tables

### Supplementary Data Table 1

Diagnostic Criteria for prediabetes/ intermediate hyperglycemia used for inclusion into DPPOS or DaQingDPOS:

ADA and WHO definition; values below these parameters can be considered NGR. Per ADA definition, HbA1c, FPG, and 2h PG needed to reach normoglycemia in parallel to be considered as in remission, Per WHO definition, FPG, and 2h PG needed to reach normoglycemia in parallel to be considered as in remission,

Test	ADA (American Diabetes Association)	WHO (World Health Organization)
Fasting Plasma Glucose (FPG)	100–125 mg/dL (5.6–6.9 mmol/L)	110–125 mg/dL (6.1–6.9 mmol/L)
2-hour Plasma Glucose (OGTT)	140–199 mg/dL (7.8–11.0 mmol/L)	140–199 mg/dL (7.8–11.0 mmol/L)
HbA1c	5.7–6.4% (39–46 mmol/mol)	Not recommended

**Supplementary Data Table 2.** Comparing overall events and follow-up times for all DPPOS participants according to remission and non-remission (ADA criteria) after 1 year of intervention

	Remission (n=275)	Non-remission (n=2127)
Follow-up time for diabetes diagnosis in years, median (IQR)	15.0 (8.0, 21.5)	8.2 (3.5, 19.0)
Diabetes cases during follow-up, n (%)	93 (34)	1209 (57)
PY for diabetes during follow-up, total years	3944	22364
Diabetes incidence rate/100 PY	2.36	5.41
Follow-up time for composite endpoint cardiovascular death or hospitalization for heart failure in years, median (IQR)	20.3 (13.5, 21.0)	20.0 (13.7, 21.0)
Follow-up time for hospitalization for heart failure, median (IQR)	20.3 (13.5, 21.0)	20.0 (13.7, 21.0)
Follow-up time for cardiovascular death, median (IQR)	20.4 (13.6, 21.0)	20.0 (13.7, 21.0)
Follow-up time for extended MACE, median (IQR)	20.0 (11.5, 21.0)	19.9 (11.0, 20.6)

Follow-up time for MACE, median (IQR)	20.1 (13.1, 21.0)	20.0 (12.9, 20.93)
Follow-up time for Mortality, median (IQR)	20.4 (14.5, 21.0)	20.0 (15.6, 21.0)

PY refers to person years. Medians and interquartile ranges for follow-up times of diabetes and cardiovascular disease endpoints are given in years.

### Supplementary Data Table 3

**DPPOS:** Descriptive characteristics of DPPOS participants according to remission or non-remission (WHO criteria) at baseline and at year 1 after randomization

Characteristic	Baseline			1 year		
	Remission (n=882)	Non-remission (n=1520)	<i>p</i> value <sup>a</sup>	Remission (n=882)	Non-remission (n=1520)	<i>p</i> value <sup>a</sup>
Age (years)	49.1 (42.6, 56.7)	50.5 (44.0, 58.4)	0.005	50.1 (43.6, 57.7)	51.5 (45.0, 59.4)	0.005
BMI (kg/m <sup>2</sup> )	32.0 (28.6, 36.4)	32.8 (28.9, 37.4)	0.009	30.2 (26.7, 34.2)	31.8 (28.2, 37.0)	<0.0001
Change in BMI (kg/m <sup>2</sup> )	--	--	--	1.5 (0.2, 3.0)	0.5 (-0.4, 1.8)	<0.0001
Weight (kg)	90.6 (80.4, 104.2)	90.9 (78.9, 104.0)	0.614	85.4 (75.0, 98.2)	88.6 (76.5, 102.2)	0.001
Fasting glucose (mmol/l)	5.7 (5.6, 6.0)	5.8 (5.6, 6.2)	<0.0001	5.4 (5.2, 5.7)	5.8 (5.4, 6.2)	<0.0001
30 min OGTT glucose (mmol/l)	9.2 (8.4, 10.0)	9.3 (8.5, 10.3)	0.0001	8.7 (7.8, 9.6)	9.5 (8.5, 10.6)	<0.0001
120 min OGTT glucose (mmol/l)	8.6 (8.2, 9.3)	9.2 (8.4, 10.0)	<0.0001	6.5 (5.7, 7.2)	9.2 (8.3, 10.4)	<0.0001
HbA <sub>1c</sub> (mmol/mol)	39.9 (36.6, 42.1)	40.4 (37.7, 43.2)	<0.0001	38.8 (35.5, 42.1)	41.0 (37.7, 43.2)	<0.0001
HbA <sub>1c</sub> (%)	5.8 (5.5, 6.0)	5.9 (5.6, 6.1)	<0.0001	5.7 (5.4, 6.0)	5.9 (5.6, 6.1)	<0.0001

Fasting insulin (pmol/l)	132.0 (96.0, 186.0)	144.0 (96.0, 204.0)	0.003		108.0 (72.0, 150.0)	126.0 (90.0, 186.0)	<0.0001
30 min OGTT insulin (pmol/l)	546.0 (366.0, 768.0)	510.0 (360.0, 714.0)	0.041		498.0 (330.0, 726.0)	492.0 (336.0, 690.0)	0.950
LDL cholesterol (mmol/l)	3.2 (2.6, 3.8)	3.2 (2.7, 3.7)	0.726		3.1 (2.5, 3.6)	3.1 (2.6, 3.7)	0.210

**Supplementary Data Table 3:** Data are median (IQR) unless indicated otherwise.

<sup>a</sup>*p* values were derived from Wilcoxon tests.

Using the WHO criteria for remission to NGR, there were 2402 participants included in this analysis. Of these 2402 participants, 882 (37%) were responders based on the WHO criteria and 1520 (63%) were non-responders. Table 1 shows descriptive statistics for these participants stratified by responder group based on WHO criteria. The median follow-up times for diabetes, composite of CV death or hosp. for HF, and extended MACE for WHO responders were 14.5 years (IQR: 6.7, 21.4), 20.1 years (IQR: 14.1, 21.0), and 20.0 years (IQR: 11.5, 20.9), respectively. The median follow-up times for diabetes, composite of CV death or HF, and extended MACE for WHO non-responders were 6.5 years (IQR: 3.0, 15.9), 20.0 years (IQR: 13.4, 20.9), and 19.9 years (IQR: 10.9, 20.6), respectively. In total 333 (38%) out of 882 WHO responders were diagnosed with diabetes by the end of DPPOS phase 3 compared to 969 (64%) of 1520 WHO non-responders.

**Supplementary Data Table 4. DPPOS:** Hazard Ratios for indicated endpoints comparing prediabetes remission to NGR (after 1 year of LI) to non-remission (WHO criteria) after 20 years of follow-up.

	Cases/person-years	Event rate/1000 person-year (95% CI)	Crude HR (95% CI)	p value	Adjusted HR* (95% CI)	p value	Adjusted HR** (95% CI)	p-value
<b>CV death or hosp. for HF</b>								
Non-remission	112/ 25125	4.46 (3.71, 5.36)	Ref		Ref		Ref	
Remission	43/ 14764	2.91 (2.16, 3.93)	0.64 (0.45, 0.91)	0.014	0.72 (0.50, 1.03)	0.073	0.75 (0.52, 1.10)	0.137
<b>Hosp. for HF</b>								
Non-remission	51/ 24953	2.04 (1.55, 2.69)	Ref		Ref		Ref	
Remission	21/ 14736	1.43 (0.93, 2.19)	0.68 (0.41, 1.14)	0.143	0.80 (0.47, 1.35)	0.395	0.96 (0.56, 1.65)	0.087
<b>CV death</b>								
Non-remission	74/ 25262	2.93 (2.33, 3.68)	Ref		Ref		Ref	
Remission	26/ 14871	1.75 (1.19, 2.57)	0.59 (0.38, 0.92)	0.020	0.66 (0.42, 1.04)	0.074	0.65 (0.40, 1.04)	0.072
<b>Extended MACE</b>								
Non-remission	245/ 23843	10.28 (9.07, 11.64)	Ref		Ref		Ref	
Remission	116/ 14024	8.27 (6.90, 9.91)	0.80 (0.64, 0.99)	0.048	0.81 (0.64, 1.02)	0.069	0.78 (0.61, 0.99)	0.037
<b>MACE</b>								
Non-remission	161/ 24690	6.52 (5.59, 7.61)	Ref		Ref		Ref	
Remission	67/ 14469	4.63 (3.65, 5.88)	0.70 (0.53, 0.94)	0.016	0.73 (0.55, 0.99)	0.039	0.68 (0.50, 0.93)	0.014
<b>Mortality</b>								
No-remission	245/ 25664	9.55 (8.43, 10.81)	Ref		Ref		Ref	
Remission	114/ 15013	7.59 (6.32, 9.12)	0.78 (0.63, 0.98)	0.032	0.84 (0.67, 1.05)	0.125	0.81 (0.64, 1.02)	0.078



**Supplementary Data Table 4:** \*aHR adjusted for sex, race/ethnicity, treatment assignment, baseline age, baseline weight, baseline smoking status, baseline use of blood pressure lowering medication, baseline use of lipid lowering medication, and \*\*aHR time dependent diabetes during follow-up.

**Supplementary Data Table 5. DPPOS** Weighted Hazard Ratios using stabilized IPTWs for indicated endpoints comparing prediabetes remission to NGR (after 1 year of LI) to non-remission (ADA criteria) after 20 years of follow up.

	<b>Weighted Crude HR (95% CI)</b>	<b>p value</b>	<b>Weighted Adjusted HR* (95% CI)</b>	<b>p value</b>
<b>CV death or hosp. for HF</b>				
Non-remission	Ref		Ref	
Remission	0.38 (0.16, 0.88)	0.024	0.39 (0.15, 0.97)	0.044
<b>Hosp. for HF</b>				
Non-remission	Ref		Ref	
Remission	0.20 (0.03, 1.43)	0.108	0.19 (0.02, 1.43)	0.106
<b>CVD death</b>				
Non-remission	Ref		Ref	
Remission	0.45 (0.18, 1.13)	0.088	0.51 (0.19, 1.39)	0.191

\*aHR adjusted for sex, race/ethnicity, treatment assignment, baseline age, baseline weight, baseline smoking status, baseline use of blood pressure lowering and lipid lowering medication.

**Supplementary Table 6: DPPOS:** Hazard Ratios (HR) of indicated endpoints according to prediabetes remission by ADA criteria reaching any remission. Any remission indicates that remission was reached at least once during follow-up for the outcome.

	Cases/person-years	Event rate/1000 person-year (95% CI)	Crude HR (95% CI)	p value	Adjusted HR* (95% CI)	p value	Adjusted HR** (95% CI)	p value
<b>CV death or Hosp. HF</b>								
No remission	110/25758	4.27	Ref		Ref		Ref	
Any remission	45/16351	2.75	0.63 (0.45, 0.89)	0.009	0.66 (0.47, 0.95)	0.023	0.43 (0.29, 0.63)	<0.0001
<b>Hosp. for HF</b>								
No remission	58/25759	2.25	Ref		Ref		Ref	
Any Remission	14/16351	0.86	0.37 (0.21, 0.66)	0.0001	0.39 (0.22, 0.71)	0.002	0.30 (0.16, 0.57)	0.0003
<b>CV death</b>								
No remission	65/26085	2.49	Ref		Ref		Ref	
Any remission	35/16467	2.13	0.84 (0.55, 1.26)	0.389	0.91 (0.60, 1.39)	0.663	0.59 (0.37, 0.94)	0.026
<b>Extended MACE</b>								
No remission	245/24715	9.91	Ref		Ref		Ref	
Any remission	116/15571	7.45	0.74 (0.59, 0.92)	0.007	0.76 (0.61, 0.95)	0.017	0.43 (0.34, 0.54)	<0.0001
<b>MACE</b>								
No remission	144/25579	5.63	Ref		Ref		Ref	
Any remission	84/16000	5.25	0.92 (0.70, 1.21)	0.547	0.98 (0.75, 1.29)	0.898	0.54 (0.40, 0.73)	<0.0001
<b>Mortality</b>								
No remission	244/26495	9.21	Ref		Ref		Ref	
Any Remission	115/16603	6.93	0.74 (0.59, 0.92)	0.008	0.76 (0.61, 0.95)	0.017	0.47 (0.37, 0.60)	<0.0001

**Supplementary Table 6:** \*aHR adjusted for sex, race/ethnicity, treatment assignment, baseline age, baseline weight, baseline smoking status, baseline use of blood pressure lowering and lipid lowering medication. \*\*HR Further adjusting for whether person developed diabetes during follow-up for the outcome, and time spent with diabetes during follow-up for the outcome.

For analyzing if reaching remission at least once was associated with long-term CV outcomes, remission was assessed annually after baseline using ADA criteria, requiring complete data on FPG, 2h-PG, and HbA1c. For each outcome, we examined whether achieving remission at least once during follow-up was associated with risk reduction over a maximum of 23 years. Only remission episodes occurring prior to an event were considered. Remission was assessed only up to the point of diabetes diagnosis, since oral glucose tolerance tests were discontinued thereafter.

**Supplementary Table 7. DPPOS:** Hazard Ratios (HR) of indicated endpoints according to prediabetes remission by WHO criteria in people reaching any remission. Any remission indicates that remission was reached at least once during follow-up for the outcome.

	Cases/person-years	Event rate/1000 person-year (95% CI)	Crude HR (95% CI)	p value	Adjusted HR* (95% CI)	p value	Adjusted HR** (95% CI)	p value
<b>CV death or Hosp. HF</b>								
No remission	63/13424	4.69	Ref		Ref		Ref	
Any remission	92/28685	3.21	0.67 (0.49, 0.92)	0.015	0.71 (0.51, 0.98)	0.039	0.27 (0.18, 0.40)	<0.0001
<b>Hosp. for HF</b>								
No remission	31/13424	2.31	Ref		Ref		Ref	
Any Remission	41/28686	1.43	0.60 (0.38, 0.96)	0.033	0.67 (0.42, 1.07)	0.095	0.34 (0.19, 0.62)	0.0004
<b>CV death</b>								
No remission	43/13616	3.16	Ref		Ref		Ref	
Any remission	57/28936	1.97	0.61 (0.41, 0.90)	0.014	0.63 (0.42, 0.95)	0.026	0.21 (0.13, 0.34)	<0.001
<b>Extended MACE</b>								
No remission	139/12966	10.72	Ref		Ref		Ref	
Any remission	222/27320	8.13	0.75 (0.60, 0.92)	0.007	0.76 (0.61, 0.94)	0.012	0.26 (0.20, 0.33)	<0.0001
<b>MACE</b>								
No remission	87/13400	6.49	Ref		Ref		Ref	
Any remission	141/28179	5.00	0.76 (0.58, 0.99)	0.042	0.79 (0.60, 1.03)	0.079	0.24 (0.17, 0.33)	<0.0001
<b>Mortality</b>								
No remission	141/13893	10.15	Ref		Ref		Ref	
Any Remission	218/29203	7.46	0.72 (0.58, 0.89)	0.002	0.71 (0.57, 0.88)	0.002	0.24 (0.19, 0.32)	<0.0001

**Supplementary Table 7**\*aHR adjusted for sex, race/ethnicity, treatment assignment, baseline age, baseline weight, baseline smoking status, baseline use of blood pressure lowering and lipid lowering medication. \*\*HR Further adjusting for whether person developed diabetes during follow-up for the outcome, and time the person spent with diabetes during follow-up for the outcome.

For analyzing if reaching remission at least once was associated with long-term CV outcomes, remission was assessed annually after baseline using WHO criteria. For each outcome, we examined whether achieving remission at least once during follow-up was associated with risk reduction over a maximum of 23 years. Only remission episodes occurring prior to an event were considered. Remission was assessed only up to the point of diabetes diagnosis, since oral glucose tolerance tests were discontinued thereafter.

**Supplementary Table 8 DaQingDPOS:** Descriptive characteristics of participants according to remission or non-remission (WHO criteria) at baseline and at end of LI (6 years).

Characteristic	Baseline			6 years		
	Remission n=93	Non-remission n=447	P value	Remission n=93	Non-remission n=447	P value
Age (years)	43 (37,51)	45 (39,51)	0.203	49 (43,57)	51 (45,57)	0.203
Sex (male n%)	60 (63.8%)	238 (53.4%)	0.064	60 (63.8%)	238 (53.4%)	0.064
Smoking (n%)	41 (43.6%)	178 (39.9%)	0.506	-	-	-
BMI (kg/m <sup>2</sup> )	25.5 (21.3, 28.0)	26.3 (23.5, 28.5)	0.015	25.1 (22.1, 26.9)	25.5 (22.9, 27.6)	0.035
BMI change (kg/m <sup>2</sup> )	-	-	-	-0.40 (-1.58, 1.18)	-0.72 (-1.89, 0.30)	0.19
SBP (mmHg)	124.0 (110.0, 140.0)	130.0 (120.0, 150.0)	0.038	120.0 (112.0, 140.0)	130.0 (120.0, 140.0)	0.046
DBP (mmHg)	80.0 (80.0, 95.0)	90.0 (80.0, 96.0)	0.567	80.0 (74.0, 90.0)	84.5 (80.0, 90.0)	0.096
FPG (mmol/L)	5.2 (4.8, 5.6)	5.6 (5.1, 6.2)	<0.001	5.2 (4.8, 5.6)	6.7 (5.8, 8.5)	<0.001
PG2h (mmol/L)	8.6 (8.1, 9.0)	8.9 (8.3, 9.7)	<0.001	6.3 (5.4, 6.9)	11.8 (9.3, 14.4)	<0.001
Fasting insulin (mU/L)	17.5 (11.0, 27.0)	21.0 (14.0, 31.0)	0.010	-	-	-
TG (mmol/L)	1.1 (0.9, 1.6)	1.6 (0.9, 2.4)	0.009	1.2 (0.9, 1.7)	1.6 (1.1, 2.6)	<0.001
TC (mmol/L)	4.9 (4.1, 5.6)	4.9 (4.4, 5.7)	0.508	4.7 (4.3, 5.3)	5.2 (4.5, 5.8)	0.075

**Supplementary Table 8:** Continuous data are presented as median (IQR), categorical data are presented as number (percentage), fasting insulin is shown with 95% CI. Abbreviations: 2hPG, 2-hour plasma glucose after 75-g oral glucose tolerance test; BMI, body mass index; DBP, diastolic blood pressure; FGP, fasting plasma glucose; TC, total cholesterol; TG, triglycerides; SBP, systolic blood pressure.

**Supplementary Data Table 9: DaQingDPOS:** Hazard Ratios of indicated endpoints comparing prediabetes remission to NGR (end of LI) to non-remission (WHO criteria) after > 30 years of follow up.

	Cases/person-years	incidence/1000 person-year (95% CI)	Crude HR (95% CI)	p value	Adjusted HR* (95% CI)	p value	Adjusted HR** (95% CI)	p value
<b>CV death or Hosp. HF</b>								
Non-remission	154/8894	17.3 (14.8, 20.3)	Ref		Ref		Ref	
Remission	21/2078	10.1 (6.6, 15.5)	0.55 (0.35, 0.87)	0.011	0.48 (0.30, 0.77)	0.003	0.51 (0.32,0.83)	0.007
<b>Hosp. HF</b>								
Non-remission	71/8878	8.0 (6.3, 10.1)	Ref		Ref		Ref	
Remission	9/2085	4.3 (2.2, 8.3)	0.46 (0.24, 0.97)	0.042	0.44 (0.21, 0.92)	0.028	0.45 (0.21, 0.95)	0.035
<b>CV death</b>								
Non-remission	127/9021	14.1 (11.8, 16.8)	Ref		Ref		Ref	
Remission	17/2086	8.1 (5.1, 13.1)	0.56 (0.34, 0.93)	0.026	0.49 (0.29, 0.83)	0.008	0.54 (0.32, 0.92)	0.024
<b>MACE</b>								
Non-remission	332/7163	46.4 (41.6, 51.6)	Ref		Ref		Ref	
Remission	52/1773	29.3 (22.3, 38.5)	0.60 (0.45, 0.81)	0.001	0.58 (0.43, 0.79)	0.001	0.65 (0.48, 0.88)	0.006
<b>Mortality</b>								
Non-remission	248/9021	27.5 (24.3, 31.1)	Ref		Ref		Ref	
Remission	33/2086	15.8 (11.2, 22.3)	0.55 (0.39, 0.80)	0.001	0.46 (0.31, 0.66)	<0.001	0.52 (0.36, 0.77)	0.001

**Supplementary Data Table 9:**\*HR adjusted for sex, intervention assignment, baseline age, smoking, baseline BMI, baseline SBP, baseline cholesterol, change of body weight at the end of 6-year LI and baseline use of medications (insulin plus oral glucose lowering



mediation, blood pressure lowering medication, lipid lowering medication). \*\*aHR, time dependent diabetes during follow up (time-dependent variable).

CV death or Hosp. HF: fatal myocardial infarction, stroke, sudden death or hospitalized heart failure; Hosp. HF: hospitalization for heart failure; CV death: fatal myocardial infarction, stroke and sudden death; MACE: fatal and non-fatal MI, stroke, sudden death and hospitalized HF, or all-cause death.

**Supplementary Data Table 10a: Meta-analysis of DPPOS and DaQingDPOS**  
Based on ADA criteria for remission

Outcome	Cases	Pooled Crude HR (95% CI)	p-value	Heterogeneity, I <sup>2</sup> (p-value)	Pooled Adjusted HR* (95% CI)	p-value	Heterogeneity, I <sup>2</sup> (p-value)	Pooled Adjusted HR** (95% CI)	p-value	Heterogeneity, I <sup>2</sup> (p-value)
CV death or Hosp. HF	307/23 (non-remission/remission)	0.48 (0.31, 0.74)	0.0008	0.0% (0.58)	0.47 (0.30, 0.72)	0.0006	0.0% (0.97)	0.50 (0.32, 0.77)	0.0017	0.0% (0.99)
Mortality	586/54 (non-remission/remission)	0.62 (0.47, 0.82)	0.0009	0.0% (0.76)	0.63 (0.47, 0.84)	0.0014	62.4% (0.10)	0.66 (0.49, 0.88)	0.0052	2.7% (0.31)

**Supplementary Data Table 10a:** All pooled HRs were estimated using fixed-effects meta-analyses with DerSimonian-Laird method of inverse variance; between-study heterogeneity was not statistically significant for any of them. I<sup>2</sup> statistics based on Cochran's Q statistic were used to quantify between-study heterogeneity.

**Supplementary Data Table 10b: Meta-analysis of DPPOS and DaQingDPOS**  
Based on WHO criteria for remission

Outcome	Cases	Pooled Crude HR (95% CI)	p-value	Heterogeneity, I <sup>2</sup> (p-value)	Pooled Adjusted HR* (95% CI)	p-value	Heterogeneity, I <sup>2</sup> (p-value)	Pooled Adjusted HR** (95% CI)	p-value	Heterogeneity, I <sup>2</sup> (p-value)
CV death or Hosp. HF	266/64 (non-remission/remission)	0.61 (0.46, 0.80)	0.0004	0.0% (0.61)	0.62 (0.46, 0.83)	0.0013	34.2% (0.22)	0.66 (0.49, 0.88)	0.0054	25.3% (0.25)
Mortality	493/147 (non-remission/remission)	0.72 (0.59, 0.86)	0.0005	60.2% (0.11)	0.64 (0.36, 1.13)	0.1251	85.4% (0.009)	0.72 (0.59, 0.88)	0.0014	70.2% (0.067)

**Supplementary Data Table 10b:** For HRs for which between-study heterogeneity was not statistically significant, pooled HRs were estimated using fixed-effects meta-analyses with DerSimonian-Laird method of inverse variance. For the HR for which between-study heterogeneity was statistically significant, the pooled HR was estimated using random-effects meta-analysis with DerSimonian-Laird method of inverse variance. I<sup>2</sup> statistics based on Cochran's Q statistic were used to quantify between-study heterogeneity.

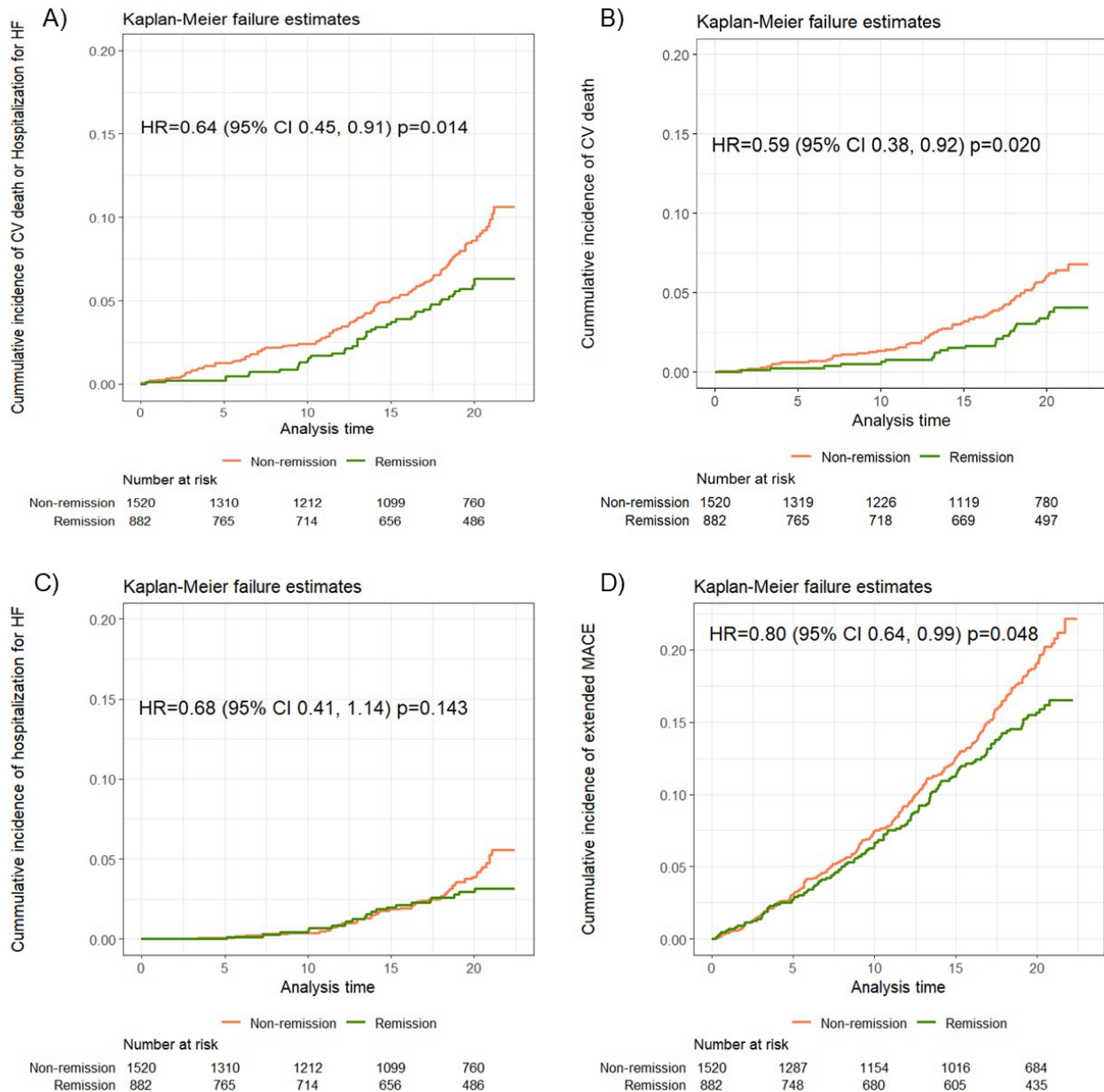
**Supplementary Data Table 11. DPPOS: FPG thresholds for preventing CV events**

<b>FPG threshold (mg/dL)</b>	<b># remission (%)</b>	<b># non-remission (%)</b>
100	1004 (42)	1398 (58)
99	902 (38)	1500 (62)
98	785 (33)	1617 (67)
97	655 (27)	1747 (73)
96	556 (23)	1846 (77)
95	454 (19)	1948 (81)
94	380 (16)	2022 (84)
93	322 (13)	2080 (87)

**Supplementary Data Table 11:** FPG thresholds (mg/dL) and the number of people achieving remission and non-remission according to those thresholds.

## Supplementary Figure 1.

DPPOS: Kaplan–Meier curves for risk of composite endpoint cardiovascular death or hospitalization for heart failure (A), cardiovascular death (B), hospitalization 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 using WHO criteria people with (orange line) and without remission (green line).

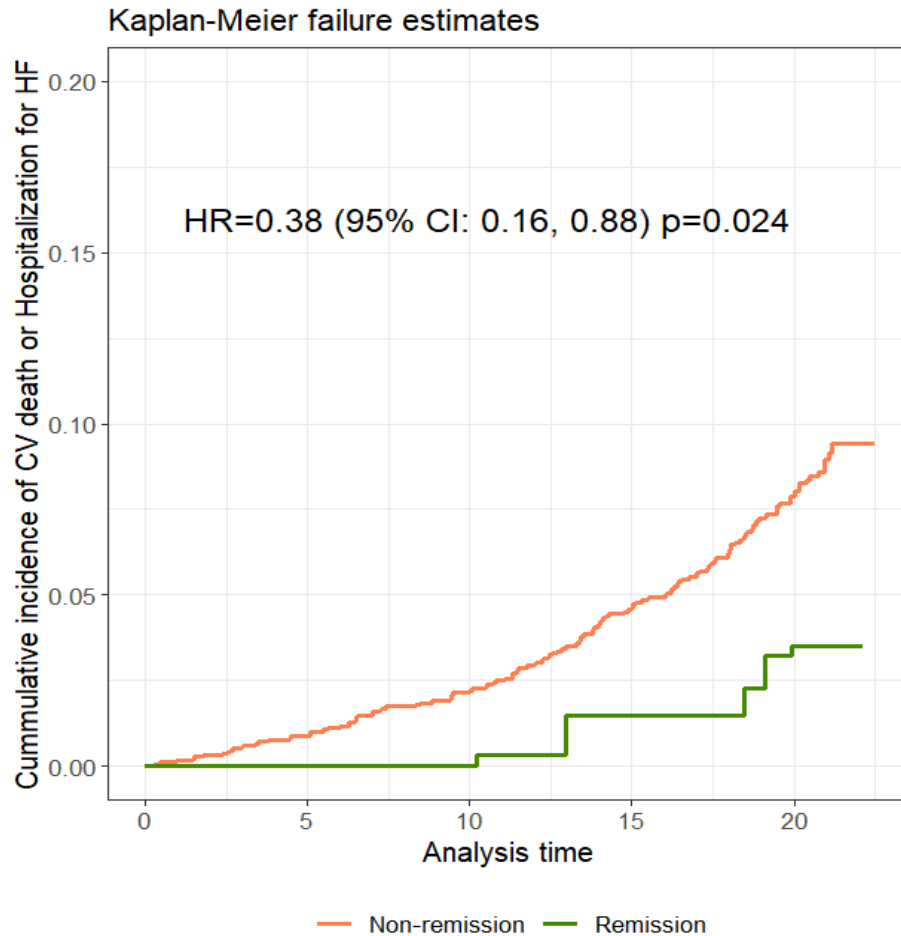


**Supplementary Figure 1:** Remission status was determined according to WHO criteria. Extended MACE included cardiovascular death, nonfatal myocardial infarction, non-fatal stroke, coronary or peripheral revascularization, hospitalization for heart failure or unstable angina, new diagnosis of coronary heart disease, or silent myocardial infarction.

DPPOS=Diabetes Prevention Program Outcomes Study. MACE=major adverse cardiovascular event.

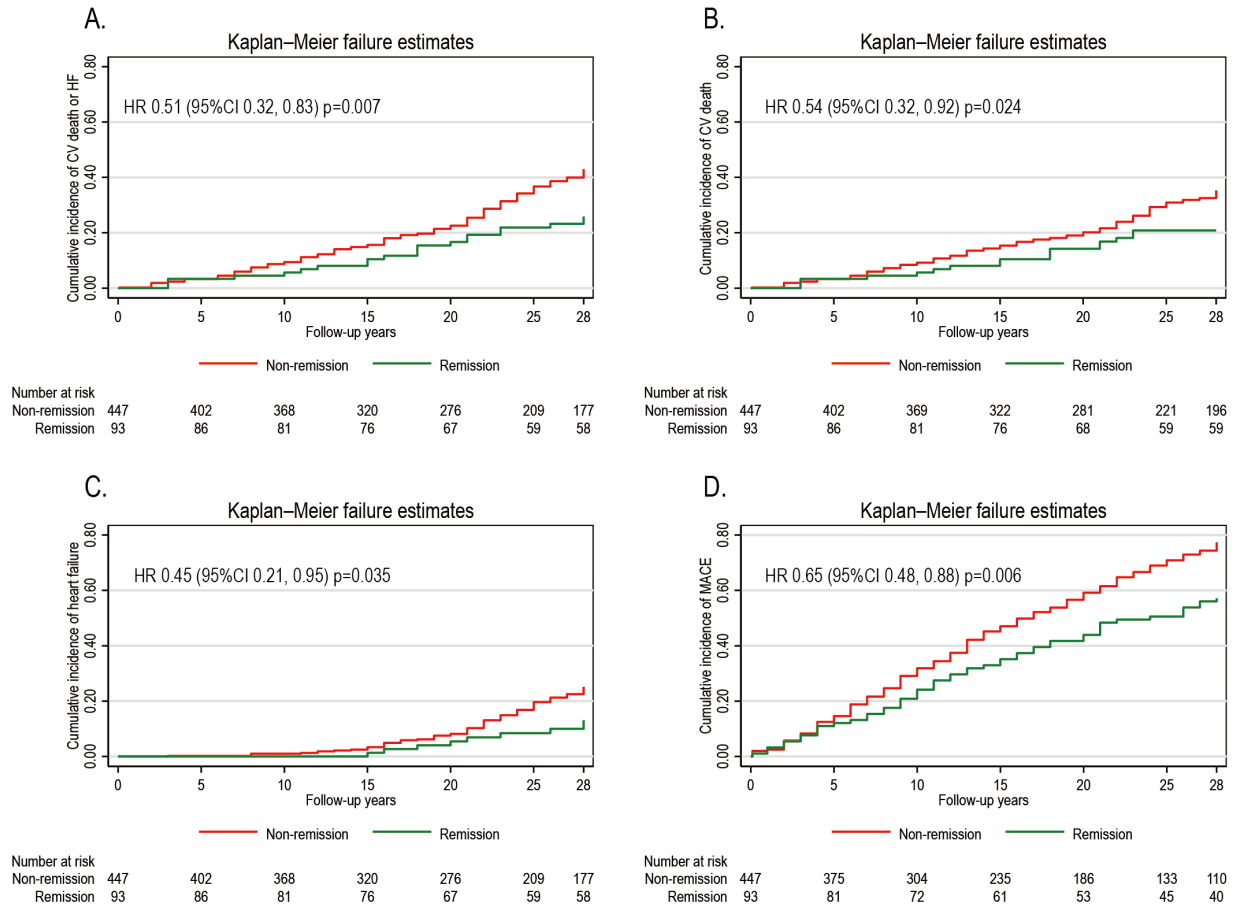
## Supplementary Figure 2.

DPPOS: Weighted Kaplan-Meier curves using stabilized IPTW's for the composite endpoint CV death or hospitalization for HF using ADA criteria for remission.



### Supplementary Figure 3.

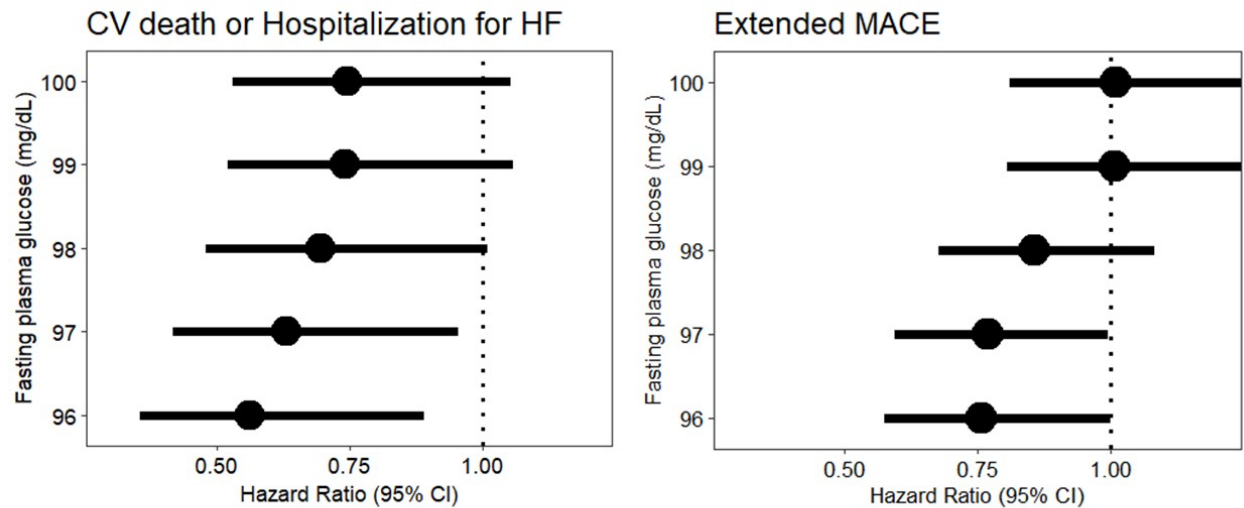
Kaplan–Meier curves for risk of composite endpoint cardiovascular death or hospitalization for heart failure (A), cardiovascular death (B), hospitalization for heart failure (C), and MACE (D) by remission status at the end of the 6-year LI over 30 years of follow up according to WHO criteria in people with (orange line) and without remission (green line).



**Supplementary Data Figure 3.** Kaplan–Meier curves for composite endpoint CV death or hospitalization for HF (A), CV Death (B), hospitalization for HF (C) and MACE including fatal and non-fatal MI, stroke, sudden death and hospitalization for HF showing groups based on remission status among participants according to WHO criteria. HRs calculated from Cox proportional -hazards analyses adjusted for age, sex, smoking, BMI, SBP, Cholesterol, intervention, change of body weight at the end of 6-year, medications and diabetes which developed after completion of 6-year intervention trial (as time-dependent variable).

#### Supplementary Figure 4.

**DPPOS:** FPG (mg/dL) thresholds for reducing risk of CV death or hospitalization for HF and extended MACE in DPPOS.



**Supplementary Figure 4.** Prediabetes remission to NGR was defined using various fasting plasma glucose (FPG) thresholds (mg/dL), and corresponding hazard ratios were assessed for the composite primary endpoint CV death or hospitalization for HF (left), and for extended MACE (right). A FPG value of  $\leq 97$ mg/dL (5.4 mmol/L) at year one in DPPOS was associated with a reduced risk of both outcomes. Comparisons were adjusted for sex, race/ethnicity, treatment assignment, baseline age, smoking status, baseline use of blood pressure- and lipid-lowering medications, and time dependent diabetes during follow-up for the outcome.

## Supplementary Appendix: Methods

### Study design DPPOS:

A detailed description of the methods is given elsewhere.<sup>1</sup> Participants were randomly assigned to metformin 850 mg twice daily, placebo twice daily, or lifestyle intervention aiming at weight reduction of  $\geq 7\%$  and at minimum 150 minutes per week of moderate intensity physical activity. Group assignment included clinical center, and the intervention was double-blinded for metformin and placebo. Basic anthropometrics such as blood pressure, height and weight and laboratory parameters such as HbA1c, insulin or lipid profiles were assessed annually as previously described.<sup>1-3</sup> The diagnosis of T2D was made based on annual OGTT or semiannual fasting glucose and was confirmed by a second test. T2D was defined based on the American Diabetes Association 1997 criteria [fasting glucose  $\geq 7.7$  mmol/l ( $\geq 125$  mg/dl) or 2-h glucose  $\geq 11.1$  mmol/l ( $\geq 200$  mg/dl)]. We defined prediabetes remission by normalizing fasting plasma glucose ( $< 5.6$  mmol/l [ $100$  mg/dl]), 2-h glucose during the OGTT ( $< 7.7$  mmol/L [ $140$  mg/dl]) and HbA1c  $< 39$  mmol/mol ( $< 5.7\%$ ) after one year of receiving the intervention (year 1 of follow-up).<sup>4-9</sup>

Management of T2D was not part of DPP and was handled by the participant's usual health care provider. Metformin or placebo were continued until a fasting plasma glucose of  $\geq 7.7$  mmol/L ( $\geq 140$  mg/dL) was reached. At the end of DPP, all surviving participants were invited to participate in DPPOS (2002 – 2020) regardless of T2D status. Participants were offered the lifestyle intervention in group sessions during the 1-year bridge period between DPP and DPPOS. During DPPOS, metformin therapy was unmasked and continued until the HbA1c was  $< 7\%$ . The decision to continue the medication was thereafter up to the care taker's decision. Similarly, during DPP and DPPOS, management of cardiovascular risk factors was up to the health care providers. All participants gave written informed consent according to the Declaration of Helsinki before screening. The DPP and DPPOS repositories contained information on 3081 of the 3234 original participants randomized to intensive lifestyle intervention, metformin, or placebo. These datasets only included information from consenting participants at clinics with institutional review board to distribute data to the repositories. Data from American Indian centers are not included. Repositories contained information on demographics, and on baseline and longitudinal measurements of anthropometrics, glucose, insulin, medication use, cholesterol, and other risk factors for diabetes and CVD. Both repositories contained data on time to diabetes diagnosis. The DPPOS repository additionally contained data on time to individual and composite components of CV morbidity and mortality. The trial was registered under NCT00038727 at clinicaltrials.gov.



### DPPOS: Participants

This analysis of prespecified endpoints of DPPOS Phase 3 includes participants from the DPP repository randomized to intensive lifestyle intervention, metformin or placebo and was conducted using data collected during DPP and during phases 1, 2, and 3 of the Diabetes Prevention Program Outcomes Study (DPPOS). There are 2402 participants included who had complete data at baseline and at year 1 after randomization on body weight, HbA1c, fasting plasma glucose, and 2-hr plasma glucose, with follow-up data on diabetes diagnosis and on CV disease events and all-cause mortality. We analyzed incidence of major atherosclerotic cardiovascular events (MACE: non-fatal heart attack, non-fatal stroke, and CV death), and extended MACE by prediabetes remission status. Participants who experienced CV disease events prior to their year 1 assessment visit during DPP were excluded from these analyses. The consort diagram is provided in the appendix (Extended Data Figure 1). Participants were classified as responders if they achieved prediabetes remission at year 1 after randomization, those who did not achieve prediabetes remission during this time were classified as non-responders.

### Endpoints: DPPOS

Adjudication of fatal and non-fatal cardiovascular events was done by a committee of physicians who were blinded to the study intervention utilizing death certificates, medical records, research records and autopsy reports. Our primary outcome for the DPPOS was the composite endpoint of CV death or hospitalization for HF. The extended MACE outcome encompassed any cardiovascular event including non-fatal myocardial infarction, non-fatal stroke, coronary or peripheral revascularization, hospitalization for congestive heart failure or unstable angina, new diagnosis of coronary heart disease or silent myocardial infarction. A detailed definition of the fatal and non-fatal events is provided in <sup>10</sup>.

At every contact, participants were screened for CV events based on criteria that have previously been applied in clinical trials<sup>10-13</sup>. New criteria for the adjudication of MI in clinical trials were established by the American Heart Association/American College of Cardiology task force and adopted by DPPOS starting Nov 2016.<sup>14</sup> Cardiac monitoring was ensured by ECG recording at baseline and annually until DPPOS year 2014 and biennially afterwards using identical electrocardiographs (MAC 1200, Marquette Electronics Inc.) at all participating study sites and recordings were evaluated centrally at the Epidemiological Cardiology Research Center of Wake Forest School of Medicine (Winston-Salem, NC). ECGs from hospital recording were evaluated using the Minnesota Code Criteria and used for adjudication.<sup>10</sup> Additionally, for participants lost to

follow-up, searches in the National Death Index with reports until Dec 31, 2018 and using a commercial investigation firm (ASG) were conducted and added to adjudication. Follow-up time includes the median three years of DPP and up to 18 years during DPPOS.

#### Inverse Probability of Treatment Weights (IPTWs) DPPOS:

We used data from 2376 DPP participants to conduct the following analyses, 26 participants from the original sample were excluded from this analysis because they had missing data on one or more covariates used to calculate the propensity scores; the CONSORT diagram for this analysis is shown in Supplementary Appendix Methods Data Figure 2 of this Appendix on page 27.

We calculated the propensity scores using logistic regression models as the probability of being a responder (remission to NGT from baseline to year 1) vs being a non-responder (no remission to NGR from baseline to year 1) based on ADA criteria. We included in the logistic regression model several baseline confounders as covariates: sex, race/ethnicity treatment assignment, age, use lipid-lowering drug therapy, whether participants had atherosclerotic vascular disease, use of antihypertensives, use of statins, smoking status, triglycerides, LDL cholesterol, total cholesterol, HDL cholesterol, weight, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, subscapular skin fold thickness, abdominal skin fold thickness, HbA1c, FPG, 2-hr PG, and physical activity levels [calculated using METs from the Low-level Physical Activity Recall (LOPAR) questionnaire]. In addition, we found that HbA1c had a cubic association with the probability of being a responder, and included linear, quadratic and cubic terms of HbA1c in the logistic regression model. We also included the following interaction terms: BMI and HbA1c, diastolic blood pressure and HbA1c, and 2-hr PG and LDL cholesterol. The logistic regression model gave the probability, or propensity score, of becoming a responder for each participant given their baseline characteristics. We used the propensity scores estimated from this logistic regression model to calculate stabilized inverse probability of treatment weights (IPTWs) for each participant.

Our final analysis included 2375 participants, 268 responders and 2107 non-responders. The stabilized IPTWs balanced all baseline participants characteristics in responders and non-responders after weighting as indicated by the standardized mean differences which had absolute values <0.15, and by the variance ratios which were also in the recommended range of 0.5 to 2. We estimated the average treatment effect of remission on each of the outcomes using weighted Cox regression models with robust sandwich variance estimators. Weighted Kaplan-Meier Curves were plotted to visualize survival differences between responders and non-responders.

Supplementary Data Table 5 of this Appendix shows results of fitting different weighted Cox regression models and Supplementary Figure 2 of this Appendix shows weighted KM curves.

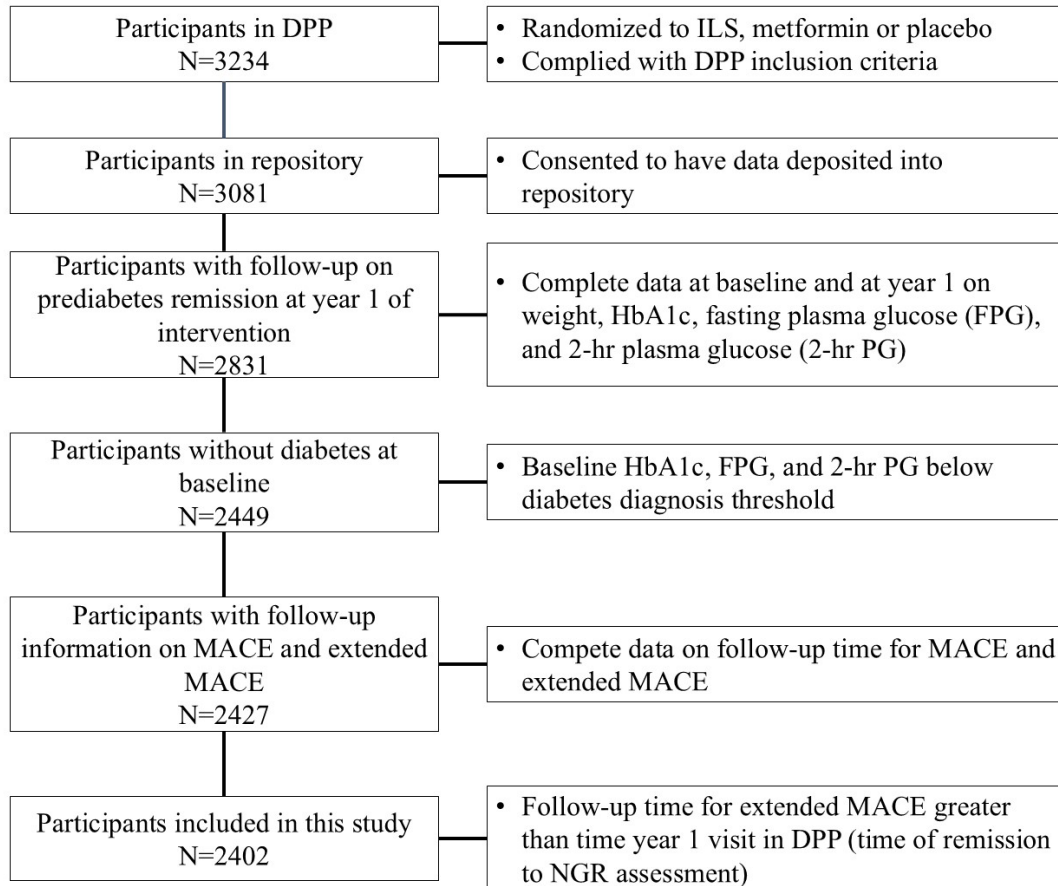
#### Study Design and Participants DaQingDPS:

In 1986, a population-based sample of 110 660 adults aged 25-74 years were screened across 33 primary care clinics in Da Qing, China. 576 participants with IGT were identified according to 1985 WHO criteria based in standard 75 g OGTT among 3956 residents with a 2-h postprandial glucose  $\geq 6.7$  mmol/L, and were cluster-randomly allocated to either a control group or one of the three lifestyle intervention group to receive a 6-year diet, exercise, or diet plus exercise intervention, respectively. People with IGT who progressed to T2D during the active intervention period were asked to accept standard diabetes care in local hospitals. After the completion of the 6-year intervention trial, all study participants transitioned to standard health care provision. In 2006 and 2016, 20 and 30 years after randomization, original participants were retraced and followed-up to determine diabetes incidence and long-term diabetes-related complications and mortality. As there were no significant differences in diabetes incidence among the three individual intervention groups during the trial, for the long-term follow-up study they were combined to a single intervention group in order to increase the power to detect differences in outcomes between the lifestyle intervention group and control group. Institutional review boards at the Chinese Center for Disease Control and Prevention and Fuwai Hospital approved the study. All study participants, or proxies who served as informants for the deceased, provided written informed consent.

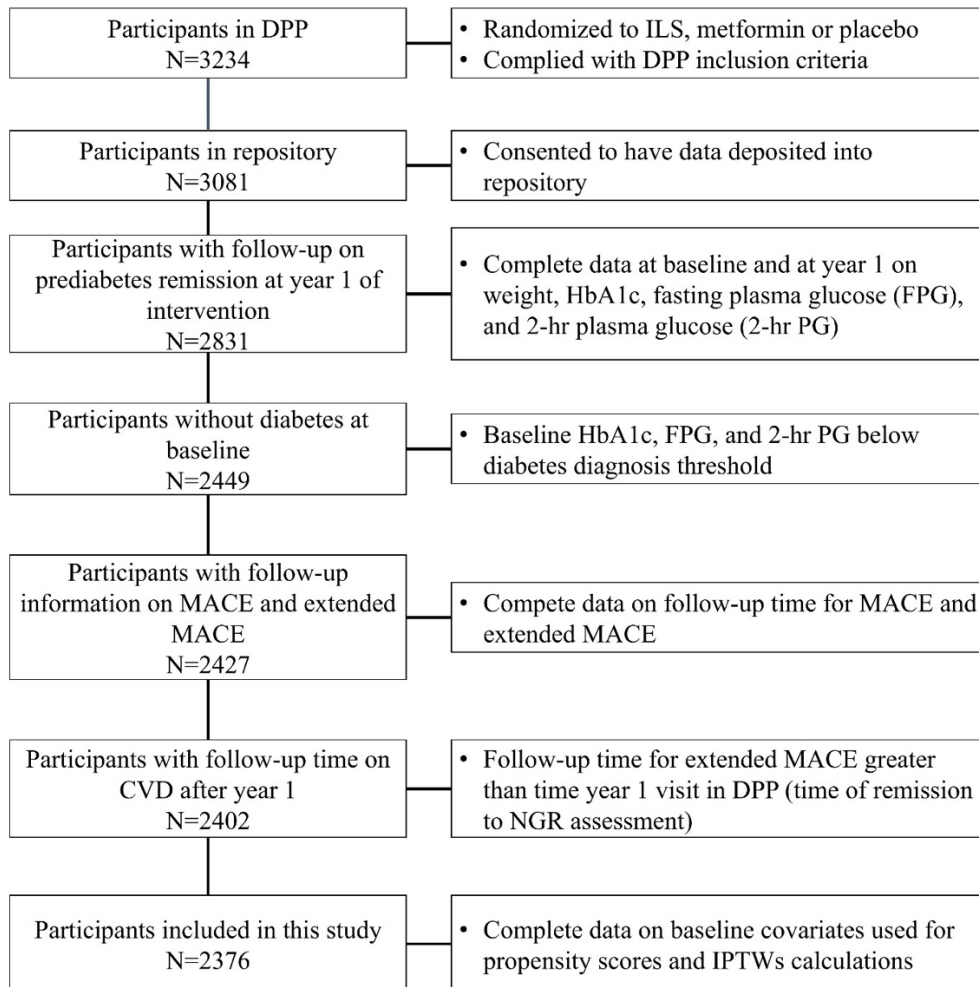
#### Endpoints: DaQingDPOS:

Diabetes was defined by 1985 WHO criteria from results of 75g OGTTs at baseline. Primary CV events were defined as non-fatal or fatal myocardial infraction or sudden death, hospitalization for heart failure, or non-fatal or fatal stroke. CV deaths were defined as deaths due to MI, sudden death, heart failure, or stroke. MACE included fatal and non-fatal MI, stroke and hospitalized HF, and all-cause death. Causes of death were determined from 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- and 30-year follow-up examinations. Two physicians, unaware of participants' trial assignments, independently adjudicated outcomes, with disagreements resolved by a third senior physician.

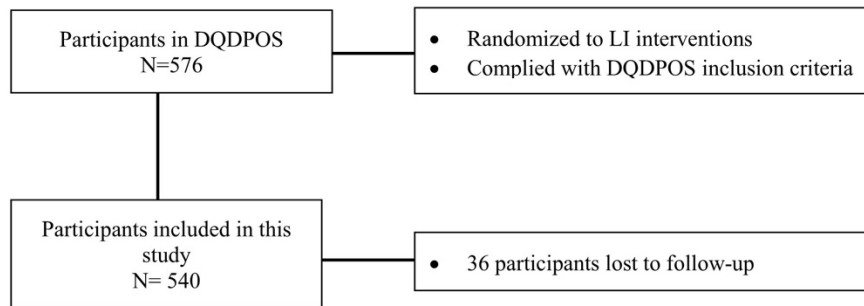
**Supplementary Appendix Methods Data Figure 1: Consort Diagram DPPOS.**



**Supplementary Appendix Methods Data Figure 2. CONSORT diagram DPPOS for analyses with IPTWs**



**Supplementary Appendix Methods Data Figure 3: Consort Diagram DaQingDPOS.**



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