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Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus (Review)

Madsen KS, Chi Y, Metzendorf MI, Richter B, Hemmingsen B

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Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus (Review)

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[Intervention Review]

Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus

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ABSTRACT

Background

The projected rise in the incidence of type 2 diabetes mellitus (T2DM) could develop into a substantial health problem worldwide. Whether metformin can prevent or delay T2DM and its complications in people with increased risk of developing T2DM is unknown.

Objectives

To assess the effects of metformin for the prevention or delay of T2DM and its associated complications in persons at increased risk for the T2DM.

Search methods

We searched the Cochrane Central Register of Controlled Trials, MEDLINE, Scopus, ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform and the reference lists of systematic reviews, articles and health technology assessment reports. We asked investigators of the included trials for information about additional trials. The date of the last search of all databases was March 2019.

Selection criteria

We included randomised controlled trials (RCTs) with a duration of one year or more comparing metformin with any pharmacological glucose-lowering intervention, behaviour-changing intervention, placebo or standard care in people with impaired glucose tolerance, impaired fasting glucose, moderately elevated glycosylated haemoglobin A1c (HbA1c) or combinations of these.

Data collection and analysis

Two review authors read all abstracts and full-text articles and records, assessed risk of bias and extracted outcome data independently. We used a random-effects model to perform meta-analysis and calculated risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, using 95% confidence intervals (CIs) for effect estimates. We assessed the certainty of the evidence using GRADE.

Main results

We included 20 RCTs randomising 6774 participants. One trial contributed 48% of all participants. The duration of intervention in the trials varied from one to five years. We judged none of the trials to be at low risk of bias in all 'Risk of bias' domains.

Our main outcome measures were all-cause mortality, incidence of T2DM, serious adverse events (SAEs), cardiovascular mortality, non-fatal myocardial infarction or stroke, health-related quality of life and socioeconomic effects. The following comparisons mostly reported only a fraction of our main outcome set.

Fifteen RCTs compared metformin with diet and exercise with or without placebo: all-cause mortality was 7/1353 versus 7/1480 (RR 1.11, 95% CI 0.41 to 3.01; $P = 0.83$; 2833 participants, 5 trials; very low-quality evidence); incidence of T2DM was 324/1751 versus 529/1881 participants (RR 0.50, 95% CI 0.38 to 0.65; $P < 0.001$; 3632 participants, 12 trials; moderate-quality evidence); the reporting of SAEs was insufficient and diverse and meta-analysis could not be performed (reported numbers were 4/118 versus 2/191; 309 participants; 4 trials; very low-quality evidence); cardiovascular mortality was 1/1073 versus 4/1082 (2416 participants; 2 trials; very low-quality evidence). One trial reported no clear difference in health-related quality of life after 3.2 years of follow-up (very low-quality evidence). Two trials estimated the direct medical costs (DMC) per participant for metformin varying from \$220 to \$1177 versus \$61 to \$184 in the comparator group (2416 participants; 2 trials; low-quality evidence).

Eight RCTs compared metformin with intensive diet and exercise: all-cause mortality was 7/1278 versus 4/1272 (RR 1.61, 95% CI 0.50 to 5.23; $P = 0.43$; 2550 participants, 4 trials; very low-quality evidence); incidence of T2DM was 304/1455 versus 251/1505 (RR 0.80, 95% CI 0.47 to 1.37; $P = 0.42$; 2960 participants, 7 trials; moderate-quality evidence); the reporting of SAEs was sparse and meta-analysis could not be performed (one trial reported 1/44 in the metformin group versus 0/36 in the intensive exercise and diet group with SAEs). One trial reported that 1/1073 participants in the metformin group compared with 2/1079 participants in the comparator group died from cardiovascular causes. One trial reported that no participant died due to cardiovascular causes (very low-quality evidence). Two trials estimated the DMC per participant for metformin varying from \$220 to \$1177 versus \$225 to \$3628 in the comparator group (2400 participants; 2 trials; very low-quality evidence).

Three RCTs compared metformin with acarbose: all-cause mortality was 1/44 versus 0/45 (89 participants; 1 trial; very low-quality evidence); incidence of T2DM was 12/147 versus 7/148 (RR 1.72, 95% CI 0.72 to 4.14; $P = 0.22$; 295 participants; 3 trials; low-quality evidence); SAEs were 1/51 versus 2/50 (101 participants; 1 trial; very low-quality evidence).

Three RCTs compared metformin with thiazolidinediones: incidence of T2DM was 9/161 versus 9/159 (RR 0.99, 95% CI 0.41 to 2.40; $P = 0.98$; 320 participants; 3 trials; low-quality evidence). SAEs were 3/45 versus 0/41 (86 participants; 1 trial; very low-quality evidence).

Three RCTs compared metformin plus intensive diet and exercise with identical intensive diet and exercise: all-cause mortality was 1/121 versus 1/120 participants (450 participants; 2 trials; very low-quality evidence); incidence of T2DM was 48/166 versus 53/166 (RR 0.55, 95% CI 0.10 to 2.92; $P = 0.49$; 332 participants; 2 trials; very low-quality evidence). One trial estimated the DMC of metformin plus intensive diet and exercise to be \$270 per participant compared with \$225 in the comparator group (94 participants; 1 trial; very-low quality evidence).

One trial in 45 participants compared metformin with a sulphonylurea. The trial reported no patient-important outcomes.

For all comparisons there were no data on non-fatal myocardial infarction, non-fatal stroke or microvascular complications.

We identified 11 ongoing trials which potentially could provide data of interest for this review. These trials will add a total of 17,853 participants in future updates of this review.

Authors' conclusions

Metformin compared with placebo or diet and exercise reduced or delayed the risk of T2DM in people at increased risk for the development of T2DM (moderate-quality evidence). However, metformin compared to intensive diet and exercise did not reduce or delay the risk of T2DM (moderate-quality evidence). Likewise, the combination of metformin and intensive diet and exercise compared to intensive diet and exercise only neither showed an advantage or disadvantage regarding the development of T2DM (very low-quality evidence). Data on patient-important outcomes such as mortality, macrovascular and microvascular diabetic complications and health-related quality of life were sparse or missing.

PLAIN LANGUAGE SUMMARY

Metformin for prevention/delay of type 2 diabetes mellitus (T2DM) and associated complications in persons at increased risk for development of T2DM

Review question

Is the antidiabetic drug metformin able to prevent or delay the development of type 2 diabetes and its associated complications in people with moderately elevated blood sugar levels?

Background

People with moderately elevated blood sugar levels (often referred to as 'prediabetes') are said to have an increased risk for developing diabetes. Metformin is a blood sugar-lowering medicine which has been used for a long time to treat people with type 2 diabetes. Type 2 diabetes, also known as adult-onset diabetes, is the most common type of diabetes and prevents the body from using insulin properly (insulin resistance). Type 2 diabetes can have bad effects on health in the long term (diabetic complications), such as severe eye or kidney disease or 'diabetic feet', eventually resulting in foot ulcers.

We investigated whether metformin can also be used to prevent or delay type 2 diabetes in people at increased risk. We examined the effects of metformin on patient-important outcomes, such as complications of diabetes, death from any cause, health-related quality of life and side effects of the drug.

Study characteristics

To be included, people had to have blood sugar levels higher than normal, but below the levels that are used to diagnose diabetes. We found 20 randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) with a total of 6774 participants. The comparator group consisted of diet and exercise, intensive diet and exercise or another blood sugar-lowering drug. One study dominated the evidence (48% of the total number of all participants). Twelve studies were performed in China. We only included studies with a treatment duration of one year or more. The treatment duration in the included studies varied from one to five years.

This evidence is up to date as of March 2019.

Key results

Fifteen studies compared metformin against diet and exercise. Eight studies compared metformin against intensive diet and exercise and three studies compared metformin plus intensive diet and exercise against intensive diet and exercise only. When compared to standard diet and exercise metformin slightly reduces or delays development of diabetes. However, when compared to intensive diet and exercise, metformin does not provide an additional benefit in reducing or delaying development of diabetes.

Seven studies compared metformin with another glucose-lowering drug: three studies compared metformin with acarbose. Three studies compared metformin with a thiazolidinedione (such as pioglitazone). There was neither an advantage or disadvantage when comparing metformin with these drugs with respect to the development of diabetes. One study compared metformin with a sulphonylurea (gliclazide). The trial did not report patient-important outcomes.

In general, the reporting of serious side effects was sparse. Few participants died and we did not detect a clear difference between the intervention and comparator groups. We also did not detect an advantage or disadvantage of metformin in relation to health-related quality of life. Our included studies did not report on non-fatal heart attacks, strokes or complications of diabetes such as kidney or eye disease. Few studies estimated the direct medical costs. When compared to diet and exercise, metformin was more expensive. When compared to intensive diet and exercise, metformin was less expensive.

We identified 11 ongoing studies which potentially could provide data for this review. These studies will add a total of 17,853 participants in future updates of our review.

Future studies should investigate more patient-important outcomes such as complications of diabetes and especially the side effects of the drugs. We do not know whether 'prediabetes' is just a condition defined by laboratory measurements, or whether it is in fact a real risk factor for diabetes. It is also unknown whether treatment of this condition translates into better patient-important outcomes.

Certainty of the evidence

All included studies had problems in the way they were conducted or reported.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table for metformin compared with diet and exercise or another antidiabetic drug

Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk

Population: people at increased risk for developing type 2 diabetes

Settings: outpatients

Intervention: metformin

Comparison: diet and exercise or a non-metformin blood glucose-lowering drug

Outcomes	Diet and exercise or a non-metformin blood glucose lowering drug	Metformin	Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
All-cause mortality (N)						
Placebo or diet and exercise Follow-up: 1 to 5 years	5 per 1000	5 per 1000 (2 to 14)	RR 1.11 (0.41 to 3.01)	2833 (5)	⊕⊕⊕⊕ very low^a	
Intensive diet plus exercise Follow-up: 1 to 5 years	3 per 1000	5 per 1000 (2 to 16)	RR 1.61 (0.50 to 5.23)	2550 (4)	⊕⊕⊕⊕ very low^a	
Sulphonylurea	Not reported					
Acarbose Follow-up: 5 years	See comment			89 (1)	⊕⊕⊕⊕ very low^b	1/44 participants in the metformin group compared with 0/45 in the acarbose group died (Fang 2004)
Thiazolidinediones	Not reported					
Incidence of type 2 diabetes mellitus (N)						
Placebo or diet and exercise Diagnostic criteria:	281 per 1000	141 per 1000 (107 to 183)	RR 0.50 (0.38 to 0.65)	3632 (12)	⊕⊕⊕⊕ moderate^c	

<ul style="list-style-type: none"> • 3 trials applied the WHO 1985 criteria (FPG <7.8 mmol/L and 2-hour glucose \geq7.8 mmol/L and <11.1 mmol/L after a 75 g OGTT) (Fang 2004; Li 1999; Lu 2002). • 5 trials applied the WHO 1999 criteria (FPG \geq7.0 mmol/L and/or a 2-hour glucose \geq11.1 mmol/L after a 75 g OGTT) (Chen 2009; IDPP-1 2006; Ji 2011; Jin 2009; Zeng 2013). • 2 trials applied the ADA 1997 criteria (FPG \geq7.0 mmol/L or 2-hour glucose \geq11.1 mmol/L after a 75 g OGTT (i.e. identical to WHO 1999 criteria) (DPP/DPPOS 2002; Wang 2009). • 1 trial applied the ADA 2009 criteria (FPG 5.6 mmol/L to 6.9 mmol/L or 2-hour glucose 7.8 mmol/L to 11.1 mmol/L) (Lu 2010). • 1 trial applied the IFG criteria of ADA 2009 (FPG 5.6 mmol/L to 6.9 mmol/L) or a HbA1c of 5.7% to 6.4% (PREVENT-DM 2017) <p>Follow-up: 1 to 5 years</p>					
<p>Intensive diet plus exercise</p> <p>Diagnostic criteria:</p> <ul style="list-style-type: none"> • 1 trial applied the WHO 1985 criteria (FPG < 7.8 mmol/L and 2-hour glucose \geq 7.8 mmol/L and < 11.1 mmol/L) (Fang 2004) • 3 trials applied the WHO 1999 criteria (FPG \geq 7.0 mmol/L and/or a 2-hour glucose \geq 11.1 mmol/L after a 75 g OGTT) (IDPP-1 2006; Ji 2011; Li 2009). • 1 trial applied the ADA 1997 criteria (FPG \geq 7.0 mmol/L or 2-hour glucose \geq 11.1 mmol/L after a 75 g OGTT (i.e. identical to WHO 1999 criteria) (DPP/DPPOS 2002). 	<p>167 per 1000</p>	<p>133 per 1000 (78 to 228)</p>	<p>RR 0.80 (0.47 to 1.37)</p>	<p>2960 (7)</p>	<p>⊕⊕⊕⊖ moderate^c</p>

<ul style="list-style-type: none"> 1 trial applied the IFG criteria of ADA 2009 (FPG 5.6 mmol/L to 6.9 mmol/L) or a HbA1c 5.7% to 6.4% (PREVENT-DM 2017) No medical association recommended the cut-off points applied in Maji 2005 to diagnose intermediate hyperglycaemia. <p>Follow-up: 1 to 5 years</p>						
Sulphonylurea	Not reported					
<p>Acarbose</p> <p>Diagnostic criteria:</p> <ul style="list-style-type: none"> 1 trial applied the WHO 1985 criteria (FPG < 7.8 mmol/L and 2-hour glucose ≥ 7.8 mmol/L and < 11.1 mmol/L) (Fang 2004). 1 trial applied the WHO 1999 criteria (FPG ≥ 7.0 mmol/L and/or a 2-hpur glucose ≥ 11.1 mmol/L after a 75 g OGTT) (Liao 2012). No medical association recommended the cut-off points applied in Maji 2005 to diagnose intermediate hyperglycaemia. <p>Follow-up: 1 to 5 years</p>	47 per 1000	81 per 1000 (34 to 196)	RR 1.72 (0.72 to 4.14)	295 (3)	⊕⊕○○	low^d
<p>Thiazolidinediones</p> <p>Diagnostic criteria:</p> <ul style="list-style-type: none"> 2 trials applied the WHO 1999 criteria (FPG ≥ 7.0 mmol/L and/or a 2-hour glucose ≥ 11.1 mmol/L after a 75 g OGTT) (Jin 2009; Zeng 2013). No medical association recommended the cut-off points applied in Maji 2005 to diagnose intermediate hyperglycaemia. <p>Follow-up: 2 to 3 years</p>	57 per 1000	56 per 1000 (23 to 136)	RR 0.99 (0.41 to 2.40)	320 (3)	⊕⊕○○	low^d 1 trial reported that no participant developed T2DM (Maji 2005)

Serious adverse events (SAE)				
<p>Placebo or diet and exercise</p> <p>Follow-up: 1 to 5 years</p>	See comment	309 (4)	⊕⊕⊕⊕ very low^e	<p>The reporting of SAE was insufficient</p> <p>1 trial reported no SAE in 29 participants in the metformin group and 30 participants in the standard care group (PREVENT-DM 2017)</p> <p>In 1 trial 3/45 participants in the metformin group experienced severe gastrointestinal reactions (Jin 2009)</p> <p>In 1 trial 1/44 participants died due to liver cancer in the metformin group compared to 0/35 participants in the standard care group (Fang 2004)</p> <p>In 1 trial 1/75 participants in the standard care group died due to cerebral thrombosis with pulmonary infection and 1/51 participants in the standard care plus fibre diet group experienced stomach cancer (Lu 2002)</p>
<p>Intensive diet plus exercises</p> <p>Follow-up: 1 to 5 years</p>	See comment	139 (2)	⊕⊕⊕⊕ very low^e	<p>The reporting of SAE was sparse</p> <p>1 trial reported no SAE in 29 participants in the metformin group and 30 participants in the standard care group (PREVENT-DM 2017)</p> <p>In 1 trial 1/44 participants died due to liver cancer in the metformin group compared to 0/36 participants in the intensive exercise and diet group (Fang 2004)</p>
Sulphonylurea	Not reported			
<p>Acarbose</p> <p>Follow-up: 1 year</p>	See comment	101 (1)	⊕⊕⊕⊕ very low^e	<p>In 1 trial 1/51 participants in the metformin group experienced cerebral haemorrhage, whereas 2/50</p>

				participants in the acarbose group experienced lung cancer and hepatitis, respectively (Liao 2012)
Thiazolidinediones	See comments	86 (1)	⊕⊕⊕⊕ very low^e	In 1 trial 3/45 participants in the metformin group experienced severe gastrointestinal reactions (Jin 2009). No severe reactions were reported in the 41 participants in the thiazolidinedione group
Cardiovascular mortality				
Placebo or diet and exercise	See comment	2416 (2)	⊕⊕⊕⊕ very low^f	1 trial reported that no participant died due to cardiovascular causes (IDPP-1 2006) 1 trial reported that 1/1073 participants in the metformin group compared with 4/1082 participants in the control group died (DPP/DPPOS 2002)
Intensive diet plus exercise	See comment	2400 (2)	⊕⊕⊕⊕ very low^f	1 trial reported that no participants died due to cardiovascular causes (IDPP-1 2006) 1 trial reported that 1/1073 participants in the metformin group compared with 2/1079 participants in the intensive diet plus exercise group died from cardiovascular causes (DPP/DPPOS 2002)
Sulphonylurea	Not reported			
Acarbose	Not reported			
Thiazolidinediones	Not reported			
Non-fatal myocardial infarction/stroke				
Placebo or diet and exercise	See comments	2416 (2)	⊕⊕⊕⊕ very low^f	No trial reported data exclusively on non-fatal myocardial infarction or stroke

				<p>Non-fatal cardiovascular events occurred in 1.7% of the participants in the control group compared with 1.5% of the participants in the metformin group (DPP/DPPOS 2002)</p> <p>In the IDPP 2/133 participants in the diet and exercise group versus 0/128 participants in the metformin group had a cardiovascular event (IDPP-1 2006)</p>
<p>Intensive diet plus exercise</p> <p>Follow-up: 2.8 to 3 years</p>	See comments	2400 (2)	⊕⊕⊕⊕ very low	<p>No trial reported data exclusively on non-fatal myocardial infarction or stroke</p> <p>1 trial reported that non-fatal cardiovascular events occurred in 1.7% of the participants in the control group compared with 1.5% of the participants in the metformin group (DPP/DPPOS 2002)</p> <p>1 trial reported that 0/128 participants in the metformin group compared to 4/120 participants in the comparator group experienced cardiovascular events (IDPP-1 2006)</p>
Sulphonylurea	Not reported			
Acarbose	Not reported			
Thiazolidinediones	Not reported			
Health-related quality of life				
<p>Placebo or diet and exercise</p> <p>Description: SF-36 to evaluate the health utility index SF-6D (physical component summaries and mental component summaries)</p> <p>Minimal important difference: difference in scores between groups of at least 3%</p>	See comment	2144 (1)	⊕⊕⊕⊕ very low	<p>After a mean of 3.2 years of follow-up there was no clear difference in any of the health-related quality of life scores between the metformin group compared with the placebo group (DPP/DPPOS 2002)</p>

Follow-up: 3.2 years					
Intensive diet plus exercise	Not reported				
Sulphonylurea	Not reported				
Acarbose	Not reported				
Thiazolidinediones	Not reported				
Socioeconomic effects					
Placebo or diet and exercise					
Description: direct medical costs	The mean direct medical costs of the control groups ranged from \$61 to \$184	The mean direct medical costs in the metformin groups ranged from \$220 to \$1177	-	2416 (2)	⊕⊕⊕⊕ low^h
Follow-up: 2.8 to 3 years					DPP: \$1177 for the metformin intervention versus \$184 for the placebo group (DPP/DPPOS 2002) IDPP: \$220 for metformin group versus \$61 in the diet and exercise group (IDPP-1 2006)
Intensive diet plus exercise					
Description: direct medical costs per participant	The mean direct medical costs of the diet plus exercise groups ranged from \$225 to \$3628	The mean direct medical costs in the metformin groups ranged from \$220 to \$1177	-	2400 (2)	⊕⊕⊕⊕ low^h
Follow-up: 2.8 to 3 years					DPP: \$1177 for the metformin intervention versus \$3628 for the intensive diet plus exercise group (DPP/DPPOS 2002) IDPP: \$220 for the metformin group compared with \$225 in the intensive diet plus exercise group (IDPP-1 2006)
Sulphonylurea	Not reported				
Acarbose	Not reported				
Thiazolidinediones	Not reported				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

ADA: American Diabetes Association; **CI:** confidence interval; **DPP:** Diabetes Prevention Program; **FPG:** fasting plasma glucose; **IDDP:** Indian Diabetes Prevention Program; **OGTT:** oral glucose tolerance test; **RR:** risk ratio; **SAE:** serious adverse event; **SF-36:** Short Form 36 items questionnaire; **T2DM:** type 2 diabetes mellitus.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

*Assumed risk was derived from the event rates in the comparator groups

^aDowngraded by three levels because of risk of bias including possible publication and other bias (early termination of studies due to benefit providing the majority of data), inconsistency and imprecision - see [Appendix 15](#); [Appendix 16](#)

^bDowngraded by three levels because of risk of bias and serious risk of imprecision - see [Appendix 17](#)

^cDowngraded by one level because of other bias (early termination of studies due to benefit providing the majority of data) - see [Appendix 15](#)

^dDowngraded by two levels because of risk of bias and imprecision - see [Appendix 17](#); [Appendix 18](#)

^eDowngraded by three levels because of risk of bias including very high risk of publication and other bias and imprecision - see [Appendix 15](#); [Appendix 16](#)

^fDowngraded by three levels because of risk of bias including risk of publication and other bias - see [Appendix 15](#); [Appendix 16](#)

^gDowngraded by three levels because of serious risk of bias (performance bias, detection bias, other bias) and imprecision - see [Appendix 15](#)

^hDowngraded by two levels because of risk of bias (trial stopped early for benefit providing the majority of data) and imprecision - see [Appendix 15](#); [Appendix 16](#)

Summary of findings 2. Summary of findings table for metformin plus intensive diet and exercise compared with intensive diet and exercise

Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk

Population: people at increased risk for developing type 2 diabetes

Settings: outpatients

Intervention: metformin plus intensive diet and exercise

Comparison: intensive diet and exercise

Outcomes	Intensive diet plus exercise	Metformin plus intensive diet and exercise	Relative effect (95% CI)	No of participants (trials)	Quality of the evidence (GRADE)	Comments
All-cause mortality (N) Follow-up: 1.5 to 3 years	See comment			450 (2)	⊕○○○ very low^a	1 trial reported that 1/121 participants died in the metformin plus intensive diet plus exercise group compared to 1/120 participants in the intensive diet plus exercise group (IDPP-1 2006) 1 trial reported that 0/95 participants died in the metformin intensive diet plus exercise group compared with 0/114 participants in the intensive diet plus exercise group (Iqbal Hydrie 2012).

Incidence of type 2 diabetes mellitus (N)	289 per 1000	159 per 1000 (29 to 844)	RR 0.55 (0.10 to 2.92)	332 (2)	⊕⊕⊕⊕ very low^b
Diagnostic criteria:					
<ul style="list-style-type: none"> 2 trials applied the WHO 1999 criteria (FPG ≥7.0 mmol/L and/or a 2-hour glucose ≥11.1 mmol/L after a 75 g OGTT) (IDPP-1 2006; Zhao 2013) 					
Follow-up: 1 to 3 years					
Serious adverse events	Not reported				
Cardiovascular mortality	See comment				1 trial reported that no participant (47 participants in each intervention group) died due to cardiovascular causes (IDPP-1 2006).
Non-fatal myocardial infarction/stroke	Not reported				
Health-related quality of life	Not reported				
Socioeconomic effects			-	94 (1)	⊕⊕⊕⊕ very low^c
Description: direct medical costs per participant	The mean direct medical costs of the intensive diet and exercise group were \$225	The mean direct medical costs of the metformin plus diet and exercise group were \$270			
Follow-up: 3 years					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

*Assumed risk was derived from the event rates in the comparator groups

^aDowngraded by three levels because of risk of bias and serious risk of imprecision - see Appendix 19

^bDowngraded by three levels because of risk of bias, inconsistency and imprecision - see [Appendix 19](#)

^cDowngraded by three levels because of trial stopped early for benefit (providing the majority of data), risk of bias and imprecision - see [Appendix 19](#)

BACKGROUND

Description of the condition

'Prediabetes', 'borderline diabetes', the 'prediabetic stage', 'high risk of diabetes' or 'intermediate hyperglycaemia' (WHO/IDF 2006) are often characterised by various measurements of elevated blood glucose concentrations (such as isolated impaired fasting glucose (IFG), isolated impaired glucose tolerance (IGT), isolated elevated glycosylated haemoglobin A1c (HbA1c) or combinations thereof). These elevated blood glucose levels indicating hyperglycaemia are considered too high to be normal but below the diagnostic threshold for type 2 diabetes mellitus (T2DM). Therefore, because of the continuous spectrum from the normal to the diabetic stage a sound evidence base is needed to define thresholds for conditions of 'sub-diabetes'. It is obvious that the different terms used to describe various stages of hyperglycaemia might induce different emotional reactions, e.g. the term 'prediabetes' may imply (at least for lay persons) that the disease diabetes is unavoidable whereas (high) risk of diabetes has the positive connotation to maybe avoid the disease altogether. All of the above mentioned terms will be used throughout this systematic review, however a focus will be set on 'prediabetes' because this labelling is associated by many persons with dire consequences - despite the disputable construct of intermediate health states termed prediseases (Viera 2011). On the other side, any diagnosis of 'prediabetes' might be an opportunity to review for example eating habits and physical activity levels, thus enabling 'affected' individuals to actively change their way of life.

The most commonly used criteria to define people with a high risk of developing T2DM were established by the American Diabetes Association (ADA) and the World Health Organization (WHO). The first glycaemic measurement used to define the prediabetic stage by the US National Diabetes Data Group was IGT (NDDG 1979). IGT is based on the measurement of plasma glucose two hours after ingestion of 75 g glucose. The prediabetic range is defined as a plasma glucose level between 7.8 mmol/L to 11.1 mmol/L (140 mg/dL to 200 mg/dL) two hours after the glucose load. Studies have indicated that IGT is caused by insulin resistance and defective insulin secretion (Abdul-Ghani 2006). In 1997, the ADA and later on the WHO introduced the IFG concept to define 'prediabetes' (ADA 1997; WHO 1999). The initial definition of IFG was 6.1 mmol/L to 6.9 mmol/L (110 mg/dL to 125 mg/dL). Later on, the ADA reduced the lower threshold for defining IFG to 5.6 mmol/L (100 mg/dL) (ADA 2003). However, this lower cut-off point for IFG to define 'prediabetes' was not endorsed by the WHO (WHO/IDF 2006). IFG seems to be associated with β -cell dysfunction (impaired insulin secretion) and an increase of the hepatic glucose output (DeFronzo 1989). More recently, HbA1c has been introduced for identifying people with a high risk of developing T2DM. In 2009, the International Expert Committee (IEC) suggested the HbA1c to identify people with a high risk of T2DM. People with HbA1c measurements between 6.0% to 6.4% fulfilled this criterion (IEC 2009). Shortly after, the ADA re-defined this HbA1c level as 5.7% to 6.4% to identify people with a high risk of developing T2DM (ADA 2010). Unlike IFG and IGT, HbA1c reflects longer-term glycaemic control, i.e. how the blood glucose levels have been during the previous two to three months (Inzucchi 2012).

In 2010, the International Diabetes Federation (IDF) estimated the prevalence of IGT to be 343 million, and this number is predicted to increase to 471 million by 2035 (IDF 2013). Studies have shown

poor correlations between HbA1c and IFG/IGT (Gosmanov 2014; Selvin 2011). Besides, the various glycaemic tests do not seem to identify the same people (Gosmanov 2014; Selvin 2011). The risk of progression from 'prediabetes' to T2DM depends on the diagnostic criteria used to identify 'prediabetes'. Some people diagnosed with 'prediabetes' will never develop T2DM, and some will return to normoglycaemia. IGT is often accepted as the best glycaemic variable for 'prediabetes' to predict progression to T2DM. However, studies indicate that less than half of the people defined as prediabetic by means of IGT will develop T2DM in the following 10 years. IFG and HbA1c are both thought to predict a different risk spectrum for developing T2DM (Cheng 2006; Morris 2013). Most importantly, 'prediabetes' is commonly an asymptomatic condition, and naturally often remains 'undiagnosed' (Centers for Disease Control and Prevention 2015). Consequently, 'prediabetes' may exist before the diagnosis of T2DM is established.

It is still not clarified if any particular intervention, especially glucose-lowering drugs, should be recommended for people with 'prediabetes' (Yudkin 2014). Studies have indicated that the progression from 'prediabetes' to T2DM is reduced, or maybe just delayed with 'lifestyle' interventions (increased physical activity, dietary changes or both) (Diabetes Prevention Program 2002; Diabetes Prevention Program FU 2009; Finnish Diabetes Prevention Study Group 2001). A recent meta-analysis of 22 trials with lifestyle interventions in people with high risk of T2DM concluded that the effect of lifestyle interventions on longer-term diabetes prevention is not clarified (Dunkley 2014).

The prescription of pharmacological glucose-lowering interventions for the prevention of T2DM is not generally accepted among international diabetes associations and clinicians. Several groups of pharmacological glucose-lowering interventions have been investigated in people with 'prediabetes'. Some findings indicate that the progression from 'prediabetes' to T2DM is reduced or maybe just delayed (Diabetes Prevention Program 2002; Diabetes Prevention Program FU 2009). However, the ADA recommends metformin for people with 'prediabetes' and a body mass index (BMI) > 35 kg/m², aged < 60 years, and women with prior gestational diabetes mellitus (ADA 2015).

Description of the intervention

Metformin is a biguanide originating from the plant *Galega officinalis* (Witters 2001). First described in 1922, it was administered to humans for the first time in France in 1957. In 1972, Canada approved its use for T2DM and later, in 1994, it received approval for use in T2DM by the US Food and Drug Administration (FDA) (Corey 2007; FDA 1994).

People with T2DM are initially advised to follow behaviour-changing ('lifestyle') interventions including weight loss and increased physical activity (ADA 2019a). However, over time the majority of people with T2DM will require additional glucose-lowering pharmacological interventions. Currently, metformin is the recommended first-line, glucose-lowering medication (ADA 2019a).

The glucose-lowering effect increases with increasing doses of metformin, whether by the immediate-release or prolonged-release formulations. The maximal recommended dose of metformin is 2000 mg daily in the USA. However, the maximum recommended daily dose of metformin in Europe and in other

regions is 3000 mg. The landmark study, UK Prospective Diabetes Study (UKPDS) applied a median daily dose of 2550 mg/day in people with newly diagnosed T2DM (UKPDS 1998).

Adverse effects of the intervention

The most common adverse effects of metformin are gastrointestinal disturbances, which are reported in 20% to 30% of people using this drug. However, the gastrointestinal disturbances only necessitate discontinuation of the drug in less than 5% of the affected individuals (DeFronzo 1999).

A potential complication of metformin use is lactic acidosis, a rare, but potentially fatal, metabolic condition that can occur whenever substantial tissue hypoxia exists (Kreisberg 1980). Lactic acidosis is characterised by elevated blood lactate concentrations (exceeding 5.0 mmol/L) and decreased blood pH (less than 7.35). The mortality is estimated to be about 50% (Huang 2016). A Cochrane Review found no firm evidence of metformin being associated with an increased risk of lactic acidosis or elevated lactate levels when compared to other glucose-lowering drugs (Salpeter 2010). However, several case reports of lactic acidosis in metformin-treated people have been published subsequently (Kalantar-Zadeh 2013; Schousboe 2012).

How the intervention might work

The exact mechanism(s) of action of metformin are not clearly elucidated. However, metformin is known to alter carbohydrate metabolism by reducing basal hepatic glucose production (gluconeogenesis), improving insulin sensitivity in the liver and peripheral tissues, as well as increasing insulin-stimulated glucose uptake and utilisation in peripheral tissues (AHFS 1999). It has been proposed that its prime mode of action is via activation of the 5' adenosine monophosphate-activated protein kinase (AMPK) enzyme (Cho 2015; Duca 2015).

Why it is important to do this review

There has been an increased focus on the prevention or delay of T2DM with non-pharmacological interventions and glucose-lowering medications. Recently, one literature review (Moin 2018) and several systematic reviews (Haw 2017; Lily 2009; Moelands 2018; Pang 2018; Salpeter 2008) have been performed in people with elevated risk of T2DM. All these reviews have methodological shortcomings and applied limited search strategies. As the prevalence of intermediate hyperglycaemia is increasing, an updated review with comprehensive search and updated methodology is needed.

OBJECTIVES

To assess the effects of metformin for the prevention or delay of type 2 diabetes mellitus (T2DM) and its associated complications in persons at increased risk for the development of T2DM.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs).

Types of participants

Nondiabetic individuals at increased risk of developing T2DM, that is, diagnosed with intermediate hyperglycaemia or 'prediabetes'.

Diagnostic criteria for 'prediabetes'

To be consistent with changes in the classification of and diagnostic criteria for 'prediabetes' (impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and elevated glycosylated haemoglobin A1c (HbA1c)) over the years, the diagnosis had to be established using the standard criteria valid at the time of the trial commencing (for example ADA 1997; ADA 2010; NDDG 1979; WHO 1999). Ideally, the diagnostic criteria should have been described. If necessary, we used the trial authors' definition of 'prediabetes' but contacted trial authors for additional information. Differences of glycaemic measurements used to define 'prediabetes' may introduce substantial heterogeneity. We therefore planned to subject diagnostic criteria to a subgroup analysis.

Types of interventions

We planned to investigate the following comparisons of intervention versus control/comparator.

Intervention

- Metformin monotherapy (with or without diet, exercise or both).

Comparator

- Placebo.
- Non-pharmacological interventions (for example diet, exercise).
- Sulfonylureas (for example glibenclamide).
- α -glucosidase inhibitors (for example acarbose).
- Thiazolidinediones (for example pioglitazone).
- Meglitinides (for example repaglinide).
- Sodium-glucose co-transporter 2 inhibitors (for example empagliflozin)
- Glucagon-like peptide-1 analogues (for example liraglutide).
- Dipeptidyl peptidase-4 inhibitors (for example sitagliptin).
- Insulin.

Concomitant interventions had to be the same in intervention and control groups to establish fair comparisons.

Minimum duration of intervention

We included trials with a minimum duration of intervention of one year.

Exclusion criteria

- People diagnosed with the 'metabolic syndrome' because this is a special cohort of doubtful clinical usefulness and uncertain distinct disease entity (a composite of risk indicators such as elevated blood lipids, insulin resistance, obesity, high blood pressure).

We did not exclude trials because one or several of our primary or secondary outcome measures were not reported in the publication. In case none of our primary or secondary outcomes was reported, we included the trial and contacted the corresponding author for supplementary data. If no additional data were available, we planned to show these trials a supplementary table.

Types of outcome measures

Primary outcomes

- All-cause mortality.
- Incidence of type 2 diabetes (T2DM).
- Serious adverse events.

Secondary outcomes

- Cardiovascular mortality.
- Non-fatal myocardial infarction.
- Non-fatal stroke.
- Amputation of lower extremity.
- Blindness or severe vision loss.
- End-stage renal disease.
- Non-serious adverse events.
- Hypoglycaemia.
- Health-related quality of life.
- Time to progression to T2DM.
- Measures of blood glucose control.
- Socioeconomic effects.

Method and timing of outcome measurement

- All-cause mortality: defined as death from any cause. Measured at the end of the intervention and the end of follow-up.
- Incidence of T2DM and time to progression to T2DM: defined according to diagnostic criteria valid at the time the diagnosis was established using the standard criteria valid at the time of the trial commencing (e.g. ADA 2008; WHO 1998). If necessary, we used the trial authors' definition of T2DM. Measured at the end of the intervention and the longest reported end of follow-up.
- Serious adverse events: defined according to the International Conference on Harmonization Guidelines as any event that leads to death, that is life-threatening, required in-patient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability, and any important medical event which may have had jeopardised the patient or required intervention to prevent it (ICH 1997) or as reported in trials. Measured at any time of the intervention and during follow-up.
- Cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, amputation of lower extremity, blindness or severe vision loss, hypoglycaemia (mild, moderate, severe/serious): defined as reported in trials. Measured at the end of the intervention and at the end of follow-up.
- End-stage renal disease: defined as dialysis, renal transplantation or death due to renal disease. Measured at the end of the intervention and at the end of follow-up.
- Non-serious adverse events: defined as number of participants with any untoward medical occurrence not necessarily having a causal relationship with the intervention. Measured at the end of the intervention and at the end of follow-up.
- Health-related quality of life: defined as mental and physical health-related quality of life as separate and combined,

evaluated by a validated instrument such as Short-Form 36. Measured at the end of the intervention and at the end of follow-up.

- Measures of blood glucose control: fasting blood glucose, blood glucose two hours after ingestion of 75 g glucose and HbA1c measurements. Measured at the end of the intervention and at the end of follow-up.
- Socioeconomic effects: for example costs of the intervention, absence from work, medication consumption. Measured at the end of the intervention and at the end of follow-up.

Search methods for identification of studies

Electronic searches

We searched the following sources from inception of each database to 7 March 2019.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO) (searched 7 March 2019).
- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946 to March 06, 2019 (searched 7 March 2019).
- Scopus (searched 7 March 2019).
- ClinicalTrials.gov (searched 7 March 2019).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal (<http://apps.who.int/trialsearch/>) (searched 7 March 2019).

For detailed search strategies, see [Appendix 1](#). We continuously applied an email alert service for MEDLINE via OvidSP to identify newly published trials using the search strategy detailed in [Appendix 1](#). We placed no restrictions on the language of publication when searching the electronic databases or reviewing reference lists of identified trials.

Searching other resources

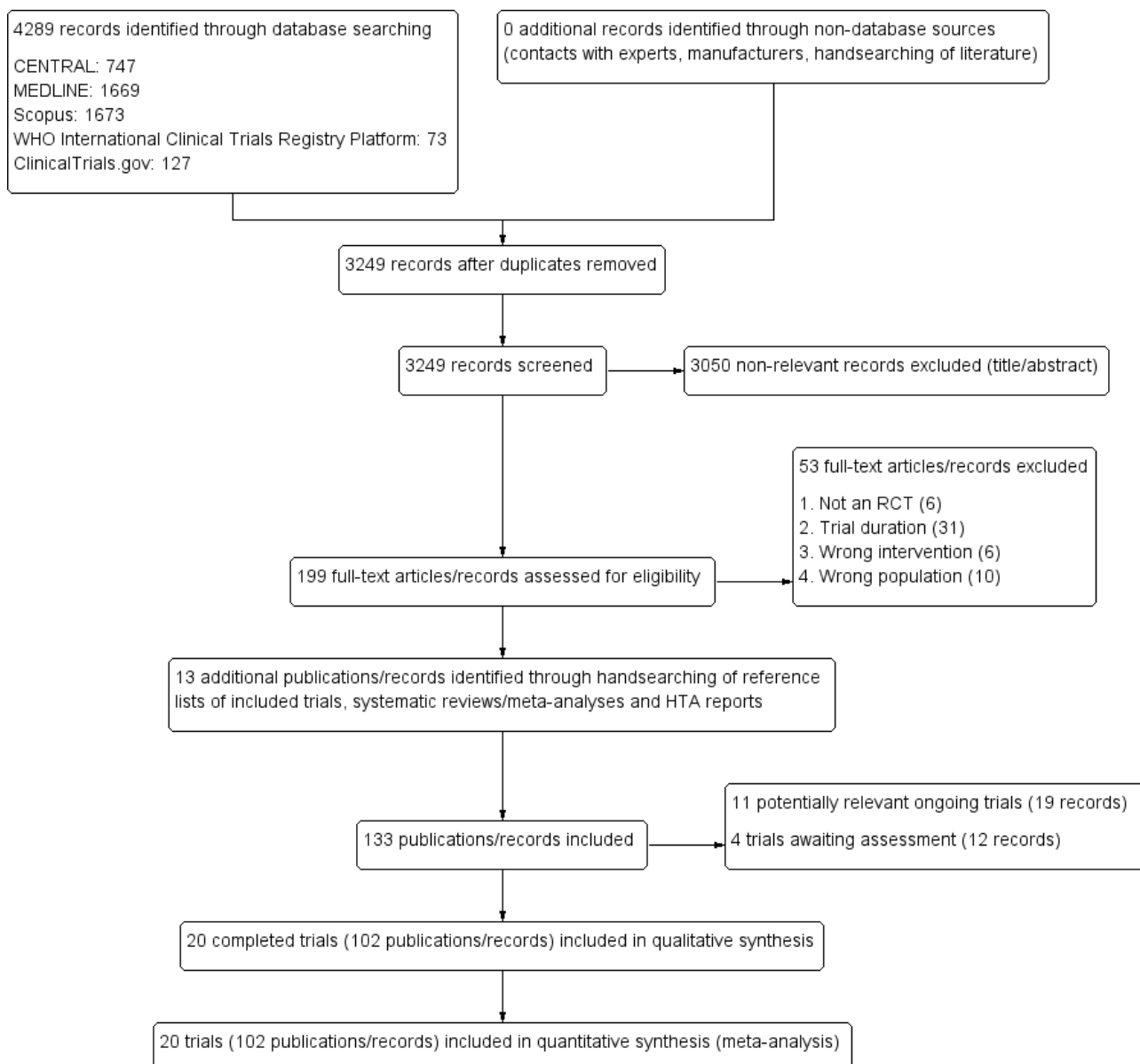
We tried to identify additional trials by searching the reference lists of included trials, (systematic) reviews, meta-analyses and health technology assessment reports. Additionally, we attempted to obtain additional trials by handsearching the most recent journal issues in print that were not indexed in the electronic databases as well. We also searched grey literature sources, which included internal reports and conference proceedings.

Data collection and analysis

Selection of studies

Two review authors independently scanned the abstract or title, or both, of records retrieved, to determine which trials should be assessed further (BR and BH). We investigated the full-text articles of all potentially relevant trials. We resolved discrepancies through consensus or by recourse to another review author (MIM). If we could not resolve a disagreement, we categorised the trial as a 'study awaiting classification' and contact the trial authors for clarification. We prepared a flow diagram of the number of trials identified and excluded at each stage in accordance with the PRISMA flow diagram of trial selection ([Liberati 2009](#); [Figure 1](#)).

Figure 1. Trial flow diagram (as of 29.05.2017, Mim)



Data extraction and management

For trials that fulfilled inclusion criteria, two review authors (KSM and BH or YC) independently extracted key participant and intervention characteristics. We reported data on efficacy outcomes and adverse events using standard data extraction sheets from the CMED Group. We resolved any disagreements by discussion or, if required, by consultation with another review author (BR) (for details see [Characteristics of included studies; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12; Appendix 13](#)).

We provided information about potentially relevant ongoing trials including trial identifier in the [Characteristics of ongoing studies](#) table and in [Appendix 7](#) 'Matrix of trial endpoint (publications and trial documents)'. For each included trial, we tried to retrieve the protocol. If not available from the search of the databases,

reference screening or Internet searches, we asked authors to provide a copy of the protocol. Predefined outcomes were entered in [Appendix 7](#).

We emailed all authors of the included trials to enquire whether they were willing to answer questions regarding their trials. We presented the results of this survey in 'Survey of trial investigators providing information on included trials' (see [Appendix 14](#)). We sought relevant missing information on the trial from the primary author(s) of the articles, if possible.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents or multiple reports of a primary trial, we maximised the information yield by collating all available data and used the most complete data set aggregated across all known publications. Duplicate publications, companion documents or multiple reports of a

primary trial were listed as secondary references under the primary reference of the included, excluded trial or ongoing trial.

Assessment of risk of bias in included studies

Review authors (KS and BH) independently assessed the risk of bias of the included trials. Studies in Chinese were assessed by one author (YC). We resolved any disagreements by consensus, or by consultation with a third review author (BH or BR). If adequate information was not available from the trial publication, trial protocol or both, we contacted trial authors for missing data on 'Risk of bias' items.

We used the Cochrane 'Risk of bias' assessment tool (Higgins 2017) assigning assessments of low, high, or unclear risk of bias (for details, see Appendix 2; Appendix 3). We evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011 according to the criteria and associated categorisations contained therein (Higgins 2017)).

Summary assessment of risk of bias

We presented a 'Risk of bias' graph and a 'Risk of bias' summary figure.

For risk of bias evaluation we grouped outcome measures as follows:

- Health-related quality of life.
- Incidence of T2DM.
- Macrovascular complications: non-fatal myocardial infarction, non-fatal stroke.
- Measures of blood glucose control.
- Microvascular complications: amputation of lower extremity, blindness/severe vision loss, end-stage renal disease
- Mortality: all-cause mortality, cardiovascular mortality.
- Non-serious adverse events (including hypoglycaemic episodes, depending on measurement).
- Serious hypoglycaemic episodes (including hypoglycaemic episodes, depending on measurement).
- Socioeconomic effects.
- Time to progression to 2DM.

We distinguished between self-reported, investigator-assessed and adjudicated outcome measures.

We defined the following outcomes as self-reported.

- Non-serious adverse events.
- Hypoglycaemia, if reported by participants.
- Health-related quality of life.
- Blood glucose control, if measured by trial participants.

We defined the following outcomes as investigator-assessed:

- All-cause mortality.
- Incidence of T2DM.
- Time to progression to T2DM.
- Serious adverse events.
- Cardiovascular mortality.
- Non-fatal myocardial infarction.

- Non-fatal stroke.
- Amputation of lower extremity.
- Blindness or severe vision loss.
- End-stage renal disease.
- Hypoglycaemia, if measured by trial personnel.
- Blood glucose control, if measured by trial personnel.
- Socioeconomic effects.

Summary assessment of risk of bias

Risk of bias for a trial across outcomes: some risk of bias domains, such as selection bias (sequence generation and allocation sequence concealment), affected the risk of bias across all outcome measures in a trial. Otherwise, we did not perform a summary assessment of the risk of bias across all outcomes for a trial. In case of high risk of selection bias, we excluded the trial.

Risk of bias for an outcome within a trial and across domains: we assessed the risk of bias for an outcome measure by including all entries relevant to that outcome (i.e. both trial-level entries and outcome-specific entries). 'Low' risk of bias was defined as low risk of bias for all key domains, 'unclear' risk of bias as unclear risk of bias for one or more key domains and 'high' risk as high risk of bias for one or more key domains.

Risk of bias for an outcome across trials and across domains: these were our main summary assessments that were incorporated in our judgements about the quality of evidence in the 'Summary of findings' tables. 'Low' risk of bias was defined as most information coming from trials at low risk of bias, 'unclear' risk of bias as most information coming from trials at low or unclear risk of bias and 'high' risk of bias as sufficient proportion of information coming from trials at high risk of bias.

Measures of treatment effect

For trials addressing the same outcome but using different outcome measure scales we planned to use standardised mean differences (SMD) with 95% CI. We planned to calculate time-to-event data as hazard ratio (HR) with 95% CI with the generic inverse variance method. Unadjusted hazard ratios were planned to be preferred, as adjustment could differ among the included trials.

The scales measuring health-related quality of life may go in different directions. Some scales increase in values with improved health-related quality of life, whereas other scales decrease in values with improved health-related quality of life. To adjust for the different directions of the scales, scales reporting better health-related quality of life with decreasing values were planned to be multiplied by -1.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome. If more than one comparison from the same trial was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison or appropriately reduced the sample size so that the same participants did not contribute multiply (splitting the 'shared' group into two or more groups). While the latter approach offers some solution to adjusting the precision of the comparison, it does

not account for correlation arising from the same set of participants being in multiple comparisons (Higgins 2011c).

We planned to reanalyse cluster randomised trials that did not appropriately adjust for potential clustering of participants within clusters in their analysis. The variance of the intervention effects would have been inflated by a design effect (DEFF). Calculation of a DEFF involves estimation of an intra-cluster correlation (ICC). Estimates of ICCs were planned to be obtained through contact with authors, or imputed using estimates from other included studies that report ICCs, or using external estimates from empirical research (e.g. Bell 2013). We planned to examine the impact of clustering using sensitivity analyses.

Dealing with missing data

If possible, we obtained missing data from trial authors and carefully evaluated important numerical data such as screened, randomly assigned participants as well as intention-to-treat (ITT), and as-treated and per-protocol populations.

We investigated attrition rates (e.g. drop-outs, losses to follow-up, withdrawals), and critically appraised issues concerning missing data and imputation methods (e.g. last observation carried forward (LOCF)).

Where means and standard deviations (SDs) for outcomes were not reported and we could not receive the needed information from trial authors, we planned to impute these values by assuming the SDs of the missing outcome to be the average of the SDs from those trials in which this information was reported.

We planned to investigate the impact of imputation on meta-analyses by performing sensitivity analyses.

Assessment of heterogeneity

We identified heterogeneity (inconsistency) by visually inspecting the forest plots and by using a standard Chi² test with a significance level of $\alpha = 0.1$ (Deeks 2017). In view of the low power of this test, we also considered the I² statistic, which quantifies inconsistency across trials, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003).

When we found heterogeneity, we attempted to determine possible reasons for this by examining individual trial and subgroup characteristics.

Assessment of reporting biases

Had we included 10 or more trials investigating a particular outcome, we planned to use funnel plots to assess small-trial effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to trial size, poor methodological design (and hence bias of small trials) and publication bias (Sterne 2017). Therefore, we planned to interpret results carefully (Sterne 2011).

Data synthesis

We planned to undertake (or display) a meta-analysis only if we judged participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure an answer that was clinically meaningful. Unless good evidence showed homogeneous effects across trials of different methodological quality, we primarily summarised low risk of bias data using a random-effects model

(Wood 2008). We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects and presented a prediction interval (Borenstein 2017a; Borenstein 2017b; Higgins 2011) for the outcome measures reported in the 'Summary of findings' tables. A prediction interval requires at least three trials to be calculated and specifies a predicted range for the true treatment effect in an individual trial (Riley 2011). For rare events such as event rates below 1%, we planned to use the Peto odds ratio method, provided there was no substantial imbalance between intervention and comparator group sizes, and intervention effects were not exceptionally large. In addition, we performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and planned to carry out subgroup analyses including investigation of interactions (Altman 2003).

- Trials designed to blind participants and investigators versus open-label trials.
- Trials with long duration (≥ 2 years) versus trials with short duration (< 2 years).
- Diagnostic 'prediabetes' criteria (IFG, IGT, HbA1c).
- Age, depending on data.
- Sex.
- Ethnicity, depending on data.
- Comorbid conditions, such as hypertension or obesity.
- Participants with previous gestational diabetes mellitus.

Sensitivity analysis

We planned to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes by restricting the analysis to:

- published trials;
- taking into account risk of bias, as specified in the [Assessment of risk of bias in included studies](#) section;
- trials using the following filters: imputation, language of publication, source of funding (industry versus other), or country.

We also planned to test the robustness of results by repeating the analysis using different measures of effect size (RR, OR, etc) and different statistical models (fixed-effect and random-effects models).

Certainty of the evidence

We presented the overall quality of the certainty for each outcome specified below, according to the GRADE approach, which takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and also to external validity, such as directness of results. Two review authors (BH and BR) independently rated the certainty of evidence for each outcome.

We included five appendices entitled 'Checklist to aid consistency and reproducibility of GRADE assessments', to help with standardisation of the 'Summary of findings' tables (Meader

2014). Alternatively, we would have used the GRADEpro Guideline Development Tool (GDT) software and presented evidence profile tables as an appendix (GRADEpro GDT 2015). We presented results for outcomes as described in the [Types of outcome measures](#) section. When meta-analysis was not possible, we presented the results in a narrative format in the 'Summary of findings' tables. We justified all decisions to downgrade the quality of trials by using footnotes, and we made comments to aid the reader's understanding of the Cochrane Review when necessary.

'Summary of findings' tables

We presented a summary of the evidence in the [Summary of findings for the main comparison](#) and the [Summary of findings 2](#). This provides key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences for each relevant comparison of alternative management strategies, numbers of participants and trials addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the 'Summary of findings' table using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011) along with Review Manager (RevMan 5.3) table editor (RevMan 2014).

Interventions presented in the 'Summary of findings' tables were metformin and metformin plus intensive diet plus exercise and comparators were diet and exercise, another blood glucose lowering drug or intensive diet plus exercise.

We reported the following outcomes, listed according to priority.

1. All-cause mortality.
2. Incidence of T2DM.
3. Serious adverse events.
4. Cardiovascular mortality.
5. Non-fatal myocardial infarction/stroke.
6. Health-related quality of life.
7. Socioeconomic effects.

RESULTS

Description of studies

For a detailed description of studies, see the '[Characteristics of included studies](#)', '[Characteristics of excluded studies](#)', and '[Characteristics of ongoing studies](#)' sections.

Results of the search

The search resulted in 4289 records, which after deduplication were reduced to 3249 records. A total of 170 references were identified as potentially eligible after screening title and abstract. Of these, 49 were excluded after checking full text. Furthermore, one publication was excluded after contact with the main author (duration of intervention less than one year) (ChiCTR-TRC-09000548), one Japanese publication was excluded after translation (not a randomised controlled trial (RCT)) (Ishida 2005) and one Chinese publication was excluded after translation (wrong intervention) (Chen 2013). Of the remaining eligible 118 records, there were 11 ongoing trials and five trials awaiting assessment. Cross-checking four systematic reviews (Haw 2017; Lily 2009; Moelands 2018; Salpeter 2008) revealed three additional references

to already included trials. One systematic review (Pang 2018) revealed a further 10 Chinese trials to be included. At the end of the process we identified 20 trials (102 records) meeting our inclusion criteria. The flowchart of records throughout the screening process is presented in [Figure 1](#).

Included studies

A detailed description of the characteristics of included trials is presented elsewhere (see [Characteristics of included studies](#) and [Appendix 4](#); [Appendix 5](#); [Appendix 6](#); [Appendix 7](#); [Appendix 8](#); [Appendix 9](#); [Appendix 10](#); [Appendix 11](#); [Appendix 12](#); [Appendix 13](#)). The following is a succinct overview.

Source of data

All but one trial reported data published in medical journals (Wang 2009). One trial was published as a conference proceeding (Wang 2009). One trial reported additional data in trial registers (DPP/DPPOS 2002). We contacted all authors or investigators of included trials by email (see [Appendix 15](#)). No additional data were provided.

Comparisons

Fifteen trials compared metformin with placebo or diet and exercise (Alfawaz 2018; BIGPRO1 2009; Chen 2009; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Jin 2009; Li 1999; Lu 2002; Lu 2010; Papoz 1978; PREVENT-DM 2017; Wang 2009; Zeng 2013). One trial compared metformin with a sulphonylurea (Papoz 1978). Three trials compared metformin with acarbose (Fang 2004; Liao 2012; Maji 2005). Three trials compared metformin with a thiazolidinediones (Jin 2009; Maji 2005; Zeng 2013). Eight trials compared metformin with intensive diet and exercise (Alfawaz 2018; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Li 2009; Maji 2005; PREVENT-DM 2017). Three trials compared metformin plus intensive diet and exercise with intensive diet and exercise (IDPP-1 2006; Iqbal Hydrie 2012; Zhao 2013). Ten trials had more than two comparison groups of relevance for this review (Alfawaz 2018; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Jin 2009; Maji 2005; Papoz 1978; PREVENT-DM 2017; Zeng 2013).

Overview of trial populations

Five trials provided information on sample size calculation (BIGPRO1 2009; DPP/DPPOS 2002; IDPP-1 2006; Iqbal Hydrie 2012; PREVENT-DM 2017). Eight of the included trials reported the total number of participants screened (BIGPRO1 2009; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Iqbal Hydrie 2012; Li 1999; Maji 2005; PREVENT-DM 2017). A total of 2426 participants were randomised to metformin. A total of 4348 participants were randomised to a comparator group. The number of randomised participants ranged from 28 to 1073 in the metformin groups and from 23 to 1082 in the comparator groups.

Trial design

All of the 20 included trials were parallel RCTs. Four trials performed blinding of the participants and investigators for one or more comparators (BIGPRO1 2009; DPP/DPPOS 2002; Li 1999; Papoz 1978), the same four trials applied placebo. Three trials reported a run-in period (DPP/DPPOS 2002; Liao 2012; Maji 2005). Two trials were terminated (DPP/DPPOS 2002; IDPP-1 2006). The duration of the intervention in the included trials varied from one year to five years. The trials were performed between the years 1969 and 2017. One trial had an extended follow-up period after the

intervention period had stopped (DPP/DPPOS 2002). Four trials were multicentre trials, defined as two or more trial centres (Alfawaz 2018; BIGPRO1 2009; DPP/DPPOS 2002; Iqbal Hydrie 2012). Twelve trials were single-centre trials (Chen 2009; Fang 2004; Ji 2011; Jin 2009; Li 2009; Liao 2012; Lu 2010; Papoz 1978; PREVENT-DM 2017; Wang 2009; Zeng 2013; Zhao 2013), and four trials did not provide the number of trial centres (IDPP-1 2006; Li 1999; Lu 2002; Maji 2005). Two trials were performed in the USA (DPP/DPPOS 2002; PREVENT-DM 2017), two trials were performed in France (BIGPRO1 2009; Papoz 1978), two trials were performed in the Middle-east (Alfawaz 2018; Iqbal Hydrie 2012), the remaining trials were performed in Asia. Three of the included trials stated that they had received commercial funding (BIGPRO1 2009; DPP/DPPOS 2002; IDPP-1 2006). Six trials had received non-commercial funding (Alfawaz 2018; Iqbal Hydrie 2012; Ji 2011; Jin 2009; Papoz 1978; PREVENT-DM 2017). One trial stated that they had received military funding (Lu 2002). Eight trials did not report the funding source (Li 1999; Li 2009; Liao 2012; Lu 2010; Maji 2005; Wang 2009; Zeng 2013; Zhao 2013).

Settings

All included trials were performed in an outpatient setting.

Participants

Fifteen trials included only people from Asia; 12 of these Chinese (Chen 2009; Fang 2004; Ji 2011; Jin 2009; Li 1999; Li 2009; Liao 2012; Lu 2002; Lu 2010; Wang 2009; Zeng 2013; Zhao 2013); two Indian (IDPP-1 2006; Maji 2005); one Pakistani (Iqbal Hydrie 2012). One trial included only Saudi Arabians (Alfawaz 2018). One trial only included Hispanic participants (PREVENT-DM 2017). One trial included mainly White participants (DPP/DPPOS 2002). Two trials did not report information about ethnicity (BIGPRO1 2009; Papoz 1978) (see Appendix 5). Five trials did not report the gender of the participants in each intervention group (Iqbal Hydrie 2012; Jin 2009; Li 2009; Maji 2005; Wang 2009). One trial included only females (PREVENT-DM 2017), and one trial included only males (Papoz 1978). For the remaining trials authors provided gender information, and both men and women were included. Four trials did not report the age of the participants (Jin 2009; Li 2009; Maji 2005; Zhao 2013). The age of the included participants varied from 41 to 65 years (see Appendix 8).

All, but five trials reported baseline fasting glucose (Iqbal Hydrie 2012; Lu 2002; Lu 2010; Wang 2009; Zhao 2013). The reported fasting glucose values at baseline varied from 5.3 mmol/L to 7.3 mmol/L. All, but four trials reported 2-hour plasma glucose after an oral glucose tolerance test (OGTT) at baseline (Alfawaz 2018; Iqbal Hydrie 2012; Lu 2010; PREVENT-DM 2017). The 2-hour plasma glucose values varied from 6.4 mmol/L to 10.4 mmol/L. Seven trials reported HbA1c values at baseline (Alfawaz 2018; DPP/DPPOS 2002; IDPP-1 2006; Li 1999; Lu 2010; Maji 2005; PREVENT-DM 2017). HbA1c varied from 5.6% to 7.6%. One trial did not report any glycaemic variables at baseline (Iqbal Hydrie 2012). All, but three trials reported body mass index (BMI) at baseline (Chen 2009; Liao 2012; Papoz 1978). BMI varied from 24 kg/m² to 35.6 kg/m².

Six trials did not report exclusion criteria (Iqbal Hydrie 2012; Ji 2011; Li 2009; Lu 2002; Maji 2005; Papoz 1978). Major exclusion criteria were diagnosis of diabetes; receiving glucose-lowering interventions and taking medications known to alter glucose tolerance; pregnant or lactating women; known renal, hepatic,

pulmonary, cardiac, cerebral, mental or endocrine disease; heavy alcohol consumption.

Diagnosis

The diagnosis applied in the included trials for identifying intermediate hyperglycaemia varied. Three trials applied the World Health Organization (WHO) 1985 diagnostic criteria for the definition of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) (fasting plasma glucose < 7.8 mmol/L and 2-hour plasma glucose after OGTT) \geq 7.8 mmol/L and < 11.1 mmol/L) (Fang 2004; Li 1999; Lu 2002). Ten trials applied the WHO 1999 criteria for the definition of IFG and/or IGT (fasting plasma glucose < 7.0 mmol/L and 2-hour plasma glucose after OGTT \geq 7.8 mmol/L and < 11.1 mmol/L) (BIGPRO1 2009; Chen 2009; IDPP-1 2006; Iqbal Hydrie 2012; Ji 2011; Jin 2009; Li 2009; Liao 2012; Zeng 2013; Zhao 2013). Two trials applied the diagnostic criteria for impaired glucose defined by American Diabetes Association (ADA) 1997 (fasting plasma glucose concentration of 5.3 mmol/L to 6.9 mmol/L and 2-hour plasma glucose after OGTT \geq 7.8 mmol/L to 11.0 mmol/L) (ADA 1997) (DPP/DPPOS 2002; Wang 2009). For the American Indian clinics in the Diabetes Prevention Program (DPP), fasting plasma glucose less than 6.9 mmol/L with no lower limit applied. Before June 1997, the criterion for plasma fasting glucose was 5.6 mmol/L to 7.7 mmol/L, or less than 7.7 mmol/L in the American Indian clinics (DPP/DPPOS 2002). A total of the 54 participants (total in all three intervention groups) included in the DPP had fasting plasma glucose above 7.0 mmol/L at baseline (DPP/DPPOS 2002). Thirteen per cent of the participants included in the DPP trial had HbA1c \geq 6.5% at baseline (DPP/DPPOS 2002). One trial applied the diagnostic criteria for impaired glucose defined by ADA 2009 (fasting plasma glucose 5.6 mmol/L to 6.9 mmol/L or 2-hour plasma glucose 7.8 mmol/L to 11.1 mmol/L) (Lu 2010). One trial only applied the IFG criteria defined by ADA 2009 (fasting plasma glucose 5.6 mmol/L to 6.9 mmol/L) or a HbA1c 5.7% to 6.4% (PREVENT-DM 2017). Most of the participants were included based on an elevated HbA1c only (67%); 13% of the participants fulfilled the inclusion criteria by IFG only; the remaining participants had both IFG and intermediate elevated HbA1c (PREVENT-DM 2017). One trial applied the diagnostic criteria for IFG defined by ADA 2017 (fasting plasma glucose 5.6 mmol/L to 6.9 mmol/L) (Alfawaz 2018). One trial applied the diagnostic criteria for impaired glucose defined by the European Diabetes Epidemiology Study Group 1970 (fasting blood glucose \geq 5.6 mmol/L and < 7.2 mmol/L or 2-hour blood glucose after OGTT \geq 6.7 mmol/L and < 8.3 mmol/L; when these criteria for intermediate hyperglycaemia were fulfilled, a second test was performed: blood glucose concentrations were determined fasting at 15, 30, 60, 120, 80, 240 and 300 minutes after an oral glucose load. Eligible individuals had 2-hour blood glucose concentrations \geq 6.7 mmol/L but < 8.3 mmol/L or fasting blood glucose concentrations \geq 5.6 mmol/L and < 7.2 mmol/L; blood glucose after 30 minutes \geq 8.9 mmol/L and < 12.2 mmol/L; blood glucose after 60 minutes \geq 8.9 mmol/L and < 12.2 mmol/L) (Papoz 1978). Another trial defined IGT as 2-hour plasma glucose after OGTT \geq 6.1 mmol/L and < 11.1 mmol/L and fasting plasma glucose < 6.1 mmol/L (Maji 2005). No medical associations recommend the cut-off points applied in the study by Maji and colleagues to diagnose intermediate hyperglycaemia (Maji 2005).

In one trial, the people with IFG and IGT were only a subset of the total randomised participants (101 out of 457 (22.1%)) (BIGPRO1 2009).

Interventions

The metformin intervention varied among the included trials; one trial applied metformin 38 mg once daily with standard diet and physical activity (Zeng 2013); one trial applied metformin 375 mg to 750 mg three times a day with no concomitant intervention (Fang 2004); one trial applied metformin 250 mg twice daily with standard diet, physical activity and education (Wang 2009); two trials applied metformin 250 mg three times a day with no concomitant intervention (Li 1999; Liao 2012); three trials applied metformin 500 mg daily with standard diet and physical activity (Alfawaz 2018; Li 2009; Maji 2005); one trial randomised the participants into two different metformin groups; one metformin group receiving 500 mg twice daily with concomitant standard diet and physical activity and one metformin group receiving 500 mg twice daily with intensive diet and physical activity (IDPP-1 2006); one trial applied metformin 500 mg twice daily with intensive diet and physical activity (Iqbal Hydrie 2012); one trial applied metformin 500 mg twice daily with standard diet, physical activity and education (Zhao 2013); two trials applied metformin 500 mg three times a day with standard diet, physical activity and education (Ji 2011; Lu 2010); one trial applied metformin 750 mg three times a day with standard diet and physical activity (Chen 2009); one trial applied metformin 750 mg three times a day with education (Lu 2002); four trials applied metformin 850 mg twice daily with standard diet and physical activity (BIGPRO1 2009; DPP/DPPOS 2002; Papoz 1978; PREVENT-DM 2017); and one trial applied metformin 1000 mg twice or three times a day with standard diet and physical activity (Jin 2009). For details see 'Description of interventions' Appendix 4

Outcomes

Three trials had specified primary outcomes (DPP/DPPOS 2002; IDPP-1 2006; PREVENT-DM 2017), all of these trials were registered at ClinicalTrials.gov (Appendix 7).

Sixteen trials reported the incidence of type 2 diabetes mellitus (T2DM) (Chen 2009; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Jin 2009; Li 1999; Li 2009; Liao 2012; Lu 2002; Lu 2010; Maji 2005; PREVENT-DM 2017; Wang 2009; Zeng 2013; Zhao 2013). Five trials reported all-cause mortality (DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Lu 2002; PREVENT-DM 2017). Sixteen trials reported 2-hour glucose values (BIGPRO1 2009; Chen 2009; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Jin 2009; Li 1999; Li 2009; Liao 2012; Lu 2002; Lu 2010; Papoz 1978; Wang 2009; Zeng 2013; Zhao 2013). Six trials reported HbA1c (Alfawaz 2018; DPP/DPPOS 2002; Ji

2011; Li 1999; Lu 2010; PREVENT-DM 2017). Eighteen trials reported fasting glucose values (Alfawaz 2018; BIGPRO1 2009; Chen 2009; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Jin 2009; Li 1999; Li 2009; Liao 2012; Lu 2002; Lu 2010; Papoz 1978; PREVENT-DM 2017; Wang 2009; Zeng 2013; Zhao 2013).

The reporting of adverse events was lacking in most trials (see Appendix 11; Appendix 12; Appendix 13).

Source of data

Where possible, we contacted all trial authors or investigators through email. If an email address was not provided in the publication we tried to contact authors by phone (see Appendix 14).

Excluded studies

We excluded 53 articles or records after full-text evaluation (Figure 1). These references are listed in Characteristics of excluded studies. We excluded 30 trials published in 31 references as they had a duration of the intervention less than one year (Acbay 1996; Ballon 2011; Biarnés 2005; Bulcão 2007; Caballero 2004; Chazova 2006; ChiCTR-TRC-09000548; Eguchi 2007; Esteghamati 2013; Flores-Saenz 2003; Gómez-Díaz 2012; Gore 2005; Kelly 2012; Kendall 2013; Kilic 2011; Koev 2004; Krysiak 2012; Lehtovirta 2001; Li 2009b; LIMIT-1; Malin 2013; Morel 1999; NCT00108615; NCT02338193; RESIST; Retnakaran 2012; SLCTR/2016/026; Stroup 2013; Sultana 2012; Wan 2010). Ten trials published in 10 references were excluded due to wrong population (Celik 2012; Fleming 2002; Gram 2011; Haukeland 2008; Kato 2009; NCT03258723; Rodríguez-Moctezuma 2005; Scheen 2009; Schuster 2004; UKPDS). Six trials published in six references were excluded due to wrong intervention (Chen 2013; Guardado-Mendoza R 2018; Lu 2011; Pre-DICTED; STOP-NIDDM; Zinman 2010). Four trials, one medical letter and one narrative review published in a total of six references were excluded as they were not RCTs (CTRI/2013/02/003417; EUCTR-000650-21-ES; EUCTR2008-004497-40-GB; Ishida 2005; Medical letter; Vitamins 2017).

Risk of bias in included studies

For details on the risk of bias of the included trials see Characteristics of included studies.

For an overview of review authors' judgements about each risk of bias item for individual trials and across all trials see Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies (blank cells indicate that the particular outcome was not measured in some trials).



group which was not blinded for the investigators and participants (DPP/DPPOS 2002).

When measured, all primary outcomes of this review were investigator-assessed and we judged these at low risk of performance and detection bias. The trials reporting blood glucose measurements were all performed by the investigators and we judged these outcomes measures at low risk of performance and detection bias.

Incomplete outcome data

All, but two trials reported the complete number of participants randomised and completing the trial (DPP/DPPOS 2002; Maji 2005).

We judged five trials to have low risk of incomplete outcome data for all outcomes reported with relevance of our review (BIGPRO1 2009; DPP/DPPOS 2002; Ji 2011; Lu 2010; PREVENT-DM 2017). We judged seven trials to have unclear risk of attrition bias for one or more outcomes (Fang 2004; IDPP-1 2006; Iqbal Hydrie 2012; Li 1999; Maji 2005; Papoz 1978; Zeng 2013). The reason for unclear risk of attrition bias were unclear or missing description of how missing data were handled, unclear whether mortality status was investigated in the people lost to follow-up and reasons for dropout were not reported. We judged eight trials to have high risk of attrition bias for one or more of the outcomes (Alfawaz 2018; Chen 2009; Jin 2009; Li 2009; Liao 2012; Lu 2002; Wang 2009; Zhao 2013). The reason for high risk of attrition bias were high dropout rate, dropout rates not balanced, reasons for dropouts not balanced, missing information on dropouts or per protocol analysis applied.

Selective reporting

We judged 15 trials as high risk of selective outcome reporting mainly because one or more outcomes of relevance for our review were likely assessed but not reported and/or the protocol were unavailable. For more details, see Figure 3, Appendix 7 and Appendix 8.

Other potential sources of bias

Seven trials appeared to be free of other potential sources of bias (Alfawaz 2018; Iqbal Hydrie 2012; Ji 2011; Jin 2009; Lu 2002; Papoz 1978; PREVENT-DM 2017). Three of the included trials stated that they had received support from a pharmaceutical company (BIGPRO1 2009; DPP/DPPOS 2002; IDPP-1 2006). Nine trials did not report the funding source (Chen 2009; Fang 2004; Li 1999; Li 2009; Lu 2010; Maji 2005; Wang 2009; Zeng 2013; Zhao 2013). It is known that trials receiving funding or provision of free drug or devices from a pharmaceutical company lead to more favourable results and conclusions than trials sponsored by other sources (Lundh 2017). Therefore, these trials were judged at unclear risk of bias in the 'other sources' bias-domain.

Effects of interventions

See: [Summary of findings for the main comparison Summary of findings table for metformin compared with diet and exercise or another antidiabetic drug](#); [Summary of findings 2 Summary of findings table for metformin plus intensive diet and exercise compared with intensive diet and exercise](#)

Baseline characteristics

For details of baseline characteristics, see [Appendix 5](#) and [Appendix 6](#).

Metformin versus placebo or diet and exercise

Fifteen trials compared metformin with diet and exercise in combination with placebo (BIGPRO1 2009; DPP/DPPOS 2002; Li 1999; Papoz 1978) or without concomitant placebo (Alfawaz 2018; Chen 2009; Fang 2004; IDPP-1 2006; Ji 2011; Jin 2009; Lu 2002; Lu 2010; PREVENT-DM 2017; Wang 2009; Zeng 2013). One trial administered metformin in doses of 38 mg/day (Zeng 2013). One trial administered metformin in doses up to 500 mg/day. One trial administered metformin in doses up to 750 mg/day (Li 1999); two trials administered metformin in doses up to 1000 mg/day (Alfawaz 2018; IDPP-1 2006); two trials administered metformin in doses up to 1500 mg/day (Ji 2011; Lu 2010); three trials administered metformin in doses up to 1700 mg/day (BIGPRO1 2009; DPP/DPPOS 2002; Papoz 1978); three trials administered metformin in doses up to 2250 mg/day (Chen 2009; Fang 2004; Lu 2002); one trial administered metformin in doses up to 2550 mg/day (PREVENT-DM 2017); and one trial administered metformin in doses up to 3000 mg/day (Jin 2009). One trial had an extended follow-up period (DPP/DPPOS 2002). Ten trials stated that the metformin group also received concomitant standard diet plus exercise (Alfawaz 2018; BIGPRO1 2009; Chen 2009; DPP/DPPOS 2002; Ji 2011; Jin 2009; Lu 2002; Lu 2010; Wang 2009; Zeng 2013). Nine trials included people of Chinese ethnicity (Chen 2009; Fang 2004; Ji 2011; Jin 2009; Li 1999; Lu 2002; Lu 2010; Wang 2009; Zeng 2013); one trial included mainly White people (DPP/DPPOS 2002); one trial included people of Saudi Arabian ethnicity (Alfawaz 2018); one trial included people of Indian ethnicity (IDPP-1 2006); one trial included Hispanic people (PREVENT-DM 2017); and two trials did not report ethnicity (BIGPRO1 2009; Papoz 1978).

Primary outcomes

All-cause mortality

Five trials reported data on all-cause mortality (DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Lu 2002; PREVENT-DM 2017).

A total of seven deaths were reported in 1353 participants in the metformin group versus seven out of 1480 participants in the comparator group (risk ratio (RR) 1.11, 95% confidence interval (CI) 0.41 to 3.01; $P = 0.83$; 2833 participants, 5 trials; very low-quality evidence; [Analysis 1.1](#)). Calculation of a 95% prediction interval was not meaningful. We did not perform subgroup analyses and sensitivity analyses due to lack of data.

Incidence of type 2 diabetes (T2DM)

Twelve trials reported data on the incidence of T2DM. The definition of T2DM varied among the included trials (see [Appendix 9](#) and [Appendix 10](#)).

A total of 324 out of 1751 participants developed T2DM in the metformin group versus 529 out of 1881 participants in the comparator group (RR 0.50, 95% CI 0.38 to 0.65; $P < 0.001$; 3632 participants, 12 trials; moderate-quality evidence; [Analysis 1.2](#)). The 95% prediction interval ranged between 0.26 and 0.97.

One trial reported the incidence of T2DM after an extended follow-up period (DPP/DPPOS 2002). At year 15, the cumulative incidence of T2DM was 560 participants (62%) in the former control group

versus 499 participants (56%) in the former metformin group (DPP/DPPOS 2002).

The funnel plot did not show small trial effect (data not shown).

Subgroup analysis: analysing trials according to blinded versus open-label trials showed interaction between subgroups indicating smaller effect sizes with blinded trials ($P = 0.003$; Analysis 1.3). Subgroup analysis according to duration of the intervention did not show interaction between subgroups ($P = 0.18$; Analysis 1.4). Subgroup analysis according to ethnicity showed interaction between subgroups indicating smaller effect sizes in White people ($P = 0.01$; Analysis 1.5). Subgroup analysis according to diagnostic criteria, age, gender, comorbid condition and previous gestational diabetes could not be performed.

Sensitivity analysis: sensitivity analysis according to publication status could not be performed as all included trials were published. Sensitivity analysis restricted to only trials with low risk of selection bias did not substantially change the effect estimate: RR 0.75, 95% CI 0.65 to 0.87; $P < 0.001$; 2155 participants, 1 trial (DPP/DPPOS 2002). Eight trials were only published in Chinese. Sensitivity analysis restricted to trials published in English did not substantially change the direction of the effect estimate: RR 0.74, 95% CI 0.65 to 0.84; $P < 0.001$; 2560 participants; 4 trials (DPP/DPPOS 2002; IDPP-1 2006; Li 1999; PREVENT-DM 2017). Sensitivity analysis excluding trials funded by a pharmaceutical company did not substantially change the direction of the effect estimate: RR 0.36, 95% CI 0.26 to 0.49; $P < 0.001$; 1216 participants; 10 trials (Chen 2009; Fang 2004; Ji 2011; Jin 2009; Li 1999; Lu 2002; Lu 2010; PREVENT-DM 2017; Wang 2009; Zeng 2013).

Serious adverse events

The reporting of serious adverse events was insufficient and diverse (very low-quality evidence). One trial reported no serious adverse events in both the intervention and comparator groups (PREVENT-DM 2017). In one trial three out of 45 participants in the metformin group experienced severe gastrointestinal reactions (Jin 2009). In one study one out of 44 participants died due to liver cancer in the metformin group compared to 0/35 participants in the standard care group (Fang 2004). In one study one out of 75 participants in the standard care group died due to cerebral thrombosis with pulmonary infection and one out of 51 participants in the standard care plus fibre diet group experienced stomach cancer (Lu 2002).

Secondary outcomes

Cardiovascular mortality

Two trials reported cardiovascular mortality (DPP/DPPOS 2002; IDPP-1 2006; very low-quality evidence). One trial reported that no participant died due to cardiovascular causes (IDPP-1 2006). One trial reported that one out of 1073 participants in the metformin group compared with four out of 1082 participants in the control group died due to cardiovascular causes (DPP/DPPOS 2002).

Non-fatal myocardial infarction

No trial reported data exclusively on non-fatal myocardial infarction (very low-quality evidence). In the DPP trial non-fatal cardiovascular events occurred in 1.7% of the participants in the control group compared with 1.5% of the participants in the metformin group (DPP/DPPOS 2002). In the Indian Diabetes Prevention Program (IDPP) trial, two out of 133 participants in the

diet and exercise group versus none out of 128 participants in the metformin group had a cardiovascular event (IDPP-1 2006).

Non-fatal stroke

None of the trials reported on non-fatal stroke (very low-quality evidence).

Amputation of lower extremity

None of the trials reported on amputation of lower extremity.

Blindness or severe vision loss

None of the trials reported on blindness or severe vision loss.

End-stage renal disease

None of the trials reported on end-stage renal disease.

Non-serious adverse events

Two trials reported on all non-serious adverse events (Lu 2010; PREVENT-DM 2017). A total of 31 out of 144 participants experienced a non-serious adverse event in the metformin group versus 17 out of 141 participants in the comparator group (RR 3.86, 95% CI 0.18 to 83.36; $P = 0.39$; 285 participants, 2 trials; Analysis 1.6). Seven trials reported partially on adverse effects (DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Jin 2009; Li 1999; Lu 2010; Wang 2009), see Appendix 11; Appendix 12; Appendix 13.

Hypoglycaemia

Three trials reported data on hypoglycaemia (IDPP-1 2006; Lu 2010; Jin 2009). One trial had two intervention arms applying metformin (metformin monotherapy and metformin plus intensive diet and exercise) (IDPP-1 2006). The number of participants with hypoglycaemia was not reported separately for each metformin group. A total of 22 out of 248 participants reported symptoms of mild hypoglycaemia. None experienced symptoms of hypoglycaemia in the comparator group (IDPP-1 2006). One trial reported that no participant experienced hypoglycaemia (Jin 2009). One trial reported that four out of 115 participants in the metformin group experienced low blood glucose compared to two out of 111 participants in the comparator group (Lu 2010).

Health-related quality of life

The DPP trial applied the Short Form (SF)-36 to evaluate the health utility index (SF-6D), physical component summaries (PCS) and mental component summaries (MCS). Minimal important difference (MID) was defined as difference in scores between groups of at least 3% (DPP/DPPOS 2002). After a mean of 3.2 years of follow-up there was no clear difference in any of the health-related quality of life scores between the metformin group compared with the placebo group (very low-quality evidence).

Time to progression to T2DM

After a median of 10 years follow-up in the DPP trial, the onset of diagnosis of T2DM was delayed by two years with metformin compared with placebo (DPP/DPPOS 2002).

Measures of blood glucose control

2-hour glucose

Thirteen trials reported data on 2-hour glucose after an oral glucose tolerance test (OGTT) (BIGPRO1 2009; Chen 2009; DPP/DPPOS 2002;

Fang 2004; IDPP-1 2006; Ji 2011; Jin 2009; Li 1999; Lu 2002; Lu 2010; Papoz 1978; Wang 2009; Zeng 2013). The effect estimate showed benefit in favour of metformin (mean difference (MD) -0.86 mmol/L; 95% CI -1.26 to -0.46; $P < 0.001$; 3346 participants; 13 trials; [Analysis 1.7](#)).

Subgroup analysis: analysing trials according to blinded versus open-label trials showed interaction between subgroups ($P = 0.03$; [Analysis 1.8](#)), however CIs overlapped. Subgroup analysis according to duration of the intervention did not indicate interaction between subgroups ($P = 0.08$; [Analysis 1.9](#)). Subgroup analysis according to ethnicity showed interaction between subgroups indicating greater effect sizes for Asian people ($P < 0.001$; [Analysis 1.10](#)). Subgroup analysis according to diagnostic criteria, age, gender, comorbid condition and previous gestational diabetes could not be performed.

Sensitivity analysis: sensitivity analysis according to publication status could not be performed as all included trials were published. Sensitivity analysis restricted to only trials with low risk of selection bias changed the direction of the effects estimate: MD 0.00 mmol/L, 95% CI -0.17 to 0.17; $P = 1.0$; 1856 participants, 1 trial ([DPP/DPPOS 2002](#)). Eight trials were only published in Chinese. Sensitivity analysis restricted to trials published in English changed the direction of the effect estimate: MD -0.48 mmol/L; 95% CI -1.11 to 0.16; $P = 0.14$; 2279 participants; 5 trials ([BIGPRO1 2009](#); [DPP/DPPOS 2002](#); [IDPP-1 2006](#); [Li 1999](#); [PREVENT-DM 2017](#)). Sensitivity analysis excluding trials funded by a pharmaceutical company did not substantially change the direction of the effect estimate: MD -0.99 mmol/L, 95% CI -1.34 to -0.64; $P < 0.001$; 1179 participants; 10 trials ([Chen 2009](#); [Fang 2004](#); [Ji 2011](#); [Jin 2009](#); [Li 1999](#); [Lu 2002](#); [Lu 2010](#); [Papoz 1978](#); [Wang 2009](#); [Zeng 2013](#)).

HbA1c

Six trials reported data on HbA1c ([Alfawaz 2018](#); [DPP/DPPOS 2002](#); [Ji 2011](#); [Li 1999](#); [Lu 2010](#); [PREVENT-DM 2017](#)) showing a MD of -0.08%; 95% CI -0.22 to 0.05; $P = 0.04$; 2467 participants; 6 trials; [Analysis 1.11](#).

Subgroup analysis: analysing trials according to blinded versus open-label trials did not show interaction between subgroups ($P = 0.11$; [Analysis 1.11](#)). Subgroup analysis according to duration of the intervention did not show interaction between subgroups ($P = 0.71$; [Analysis 1.12](#)). Subgroup analysis according to ethnicity showed interaction between subgroups indicating greater effect sizes for Asian people ($P = 0.01$; [Analysis 1.13](#)). Subgroup analysis according to diagnostic criteria, age, gender, comorbid condition and previous gestational diabetes could not be performed.

Sensitivity analysis: sensitivity analysis according to publication status could not be performed as all included trials were published. Sensitivity analysis restricted to only trials with low risk of selection bias changed the direction of the effect estimate: MD 0.00%, 95% CI -0.04 to 0.04; $P = 1.0$; 1856 participants; 1 trial ([DPP/DPPOS 2002](#)). Two trials were only published in Chinese. Sensitivity analysis restricted to trials published in English changed the direction of the effect estimate: MD -0.01%; 95% CI -0.13 to 0.07; $P = 0.74$; 2125 participants; 4 trials ([Alfawaz 2018](#); [DPP/DPPOS 2002](#); [Li 1999](#); [PREVENT-DM 2017](#)). Sensitivity analysis excluding trials funded by a pharmaceutical company did not substantially change the direction of the effect estimate: MD -0.29%, 95% CI -0.57 to -0.02; P

= 0.04; 611 participants; 5 trials ([Alfawaz 2018](#); [Ji 2011](#); [Li 1999](#); [Lu 2010](#); [PREVENT-DM 2017](#)).

Fasting plasma glucose

Fifteen trials reported data on fasting plasma glucose ([Alfawaz 2018](#); [BIGPRO1 2009](#); [Chen 2009](#); [DPP/DPPOS 2002](#); [Fang 2004](#); [IDPP-1 2006](#); [Ji 2011](#); [Jin 2009](#); [Li 1999](#); [Lu 2002](#); [Lu 2010](#); [Papoz 1978](#); [PREVENT-DM 2017](#); [Wang 2009](#); [Zeng 2013](#)); random-effects MD -0.28 mmol/L; 95% CI -0.42 to -0.13; $P = 0.0002$; 3546 participants; 15 trials; [Analysis 1.14](#). Heterogeneity was substantial ($I^2 = 82%$; $P < 0.0001$).

Subgroup analysis: analysing trials according to blinded versus open-label trials did not show interaction between subgroups ($P = 0.22$; [Analysis 1.15](#)). Subgroup analysis according to duration of the intervention did not show interaction between subgroups ($P = 0.13$; [Analysis 1.16](#)). Subgroup analysis according to ethnicity did not show any interaction between subgroups ($P = 0.67$; [Analysis 1.17](#)). Subgroup analysis according to diagnostic criteria, age, gender, comorbid condition and previous gestational diabetes could not be performed.

Sensitivity analysis: sensitivity analysis according to publication status could not be performed as all included trials were published. Sensitivity analysis restricted to only trials with low risk of selection bias changed the direction of the effect estimate; random-effects MD -0.30, 95% CI -0.39 to -0.21; $P < 0.001$; 1861 participants; 1 trial ([DPP/DPPOS 2002](#)). Eight trials were published in Chinese. Sensitivity analysis restricted to trials published in English changed the direction of the effect estimate random-effects MD -0.31 mmol/L; 95% CI -0.55 to -0.08; $P = 0.009$; 2483 participants; 7 trials ([Alfawaz 2018](#); [BIGPRO1 2009](#); [DPP/DPPOS 2002](#); [IDPP-1 2006](#); [Li 1999](#); [Papoz 1978](#); [PREVENT-DM 2017](#)). Sensitivity analysis excluding trials funded by a pharmaceutical company did not change the direction of the effect estimate random-effects MD -0.27 mmol/L, 95% CI -0.48 to -0.06; $P = 0.0002$; 1374 participants; 12 trials ([Alfawaz 2018](#); [Chen 2009](#); [Fang 2004](#); [Ji 2011](#); [Jin 2009](#); [Li 1999](#); [Lu 2002](#); [Lu 2010](#); [Papoz 1978](#); [PREVENT-DM 2017](#); [Wang 2009](#); [Zeng 2013](#)).

Socioeconomic effects

During the DPP trial the metformin intervention was substantially more expensive than the placebo intervention ([DPP/DPPOS 2002](#)). Direct medical costs of the interventions during the DPP were estimated to be \$1177 for the metformin intervention versus \$184 for the placebo group (low-quality evidence). By year 10, the direct medical costs of the intervention and non-intervention-related medical costs were lower for the metformin group than for the control group (\$27,915 versus \$28,237).

From the perspective of a health system (direct medical costs of the interventions plus direct medical costs of care outside the trial) costs were \$99,600 per quality adjusted life years (QALY)-gained with metformin compared with placebo. From the perspective of society (direct medical costs plus non medical costs (expenditures from medical treatments, but not involving purchase of medical services or products) plus indirect costs (costs to the society due to morbidity and mortality, e.g. absence from work due to medical treatment)) the costs were \$99,200 per QALY-gained with metformin compared with placebo ([DPP/DPPOS 2002](#)).

The IDPP trial estimated the direct medical costs of interventions over the three-year trial period to be \$220 per participant in the

metformin group compared with \$61 in the standard diet and physical activity group (IDPP-1 2006).

Metformin versus intensive diet plus exercise

Eight trials compared metformin with intensive diet and exercise (Alfawaz 2018; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Li 2009; Maji 2005; PREVENT-DM 2017). Two trials applied metformin in doses up to 500 mg/day (Li 2009; Maji 2005); two trials applied metformin in doses up to 1000 mg/day (Alfawaz 2018; IDPP-1 2006); one trial applied metformin in doses up to 1500 mg/day (Ji 2011); one trial applied metformin in doses up to 1700 mg/day (DPP/DPPOS 2002); one trial applied metformin in doses up to 2250 mg/day (Fang 2004); and one trial administered metformin in doses up to 2550 mg/day (PREVENT-DM 2017). Five trials stated that the metformin group received concomitant diet and exercise (Alfawaz 2018; DPP/DPPOS 2002; Ji 2011; Jin 2009; Maji 2005).

Primary outcomes

All-cause mortality

Four trials reported data on all-cause mortality (DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; PREVENT-DM 2017).

A total of seven deaths were reported in 1278 participants in the metformin group versus four out of 1272 participants in the comparator group (RR 1.61, 95% CI 0.50 to 5.23; $P = 0.43$; 2550 participants, 4 trials; very low-quality of the evidence; Analysis 2.1).

We did not perform subgroup analyses and sensitivity analyses due to lack of data.

Incidence of type 2 diabetes (T2DM)

Seven trials reported the incidence of T2DM (DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Li 2009; Maji 2005; PREVENT-DM 2017). The definition of T2DM varied among the included trials (see Appendix 9 and Appendix 10). Calculation of a 95% prediction interval was not meaningful.

A total of 304 out of 1455 participants developed T2DM in the metformin group versus 251 out of 1505 participants in the comparator group (RR 0.80, 95% CI 0.47 to 1.37; $P = 0.42$; 2960 participants, 7 trials; moderate-quality of the evidence; Analysis 2.2). The 95% prediction interval ranged between 0.18 and 3.62.

One trial reported the incidence of T2DM after an extended follow-up period (DPP/DPPOS 2002). At year 15 the cumulative incidence of T2DM was 480 participants (55%) in the former intensive diet plus physical activity group versus 499 participants (56%) in the former metformin group (DPP/DPPOS 2002).

Subgroup analysis: analysing trials according to blinded versus open-label trials could not be performed as all participants were aware of randomising to intensive diet plus exercise. Subgroup analysis according to duration of the intervention could not be performed as only one trial (without any participants developing T2DM) had a duration of intervention of less than two years (PREVENT-DM 2017). Subgroup analysis according to ethnicity showed interaction between subgroups ($P = 0.02$; Analysis 2.4), however CIs overlapped. Subgroup analysis according to diagnostic criteria, age, gender, comorbid condition and previous gestational diabetes could not be performed.

Sensitivity analysis: sensitivity analysis according to publication status could not be performed as all included trials were published. Sensitivity analysis restricted to only trials with low risk of selection bias changed the direction of the effect estimate: RR 1.51, 95% CI 1.25 to 1.81; $P < 0.001$; 2152 participants; 1 trial (DPP/DPPOS 2002). Three trials were published in Chinese. Sensitivity analysis restricted to trials published in English did not substantially change the direction of the effect estimate: RR 1.26, 95% CI 0.86 to 1.86; $P = 0.24$; 2600 participants; 4 trials (DPP/DPPOS 2002; IDPP-1 2006; Maji 2005; PREVENT-DM 2017). Sensitivity analysis excluding trials funded by a pharmaceutical company changed the direction of the effect estimate towards benefit of metformin therapy: RR 0.47, 95% CI 0.25 to 0.87; $P = 0.02$; 560 participants; 5 trials (Fang 2004; Ji 2011; Li 2009; Maji 2005; PREVENT-DM 2017).

Serious adverse events

The reporting of serious adverse events was sparse and meta-analysis could not be performed. One trial reported no serious adverse events in 29 participants in the metformin group and 30 participants in the standard care group (PREVENT-DM 2017). In one trial, one out of 44 participants died due to liver cancer in the metformin group compared to zero out of 36 participants in the standard care group (Fang 2004).

Secondary outcomes

Cardiovascular mortality

Two trials reported cardiovascular mortality (DPP/DPPOS 2002; IDPP-1 2006). One trial reported that no participants died due to cardiovascular causes (IDPP-1 2006). One trial reported that one out of 1073 participants in the metformin group compared with two out of 1079 participants in the intensive diet plus exercise group died from cardiovascular causes (DPP/DPPOS 2002).

Non-fatal myocardial infarction

No trial reported data exclusively on non-fatal myocardial infarction. One trial reported that non-fatal cardiovascular events occurred in 1.7% of the participants in the control group compared with 1.5% of the participants in the metformin group (DPP/DPPOS 2002). One trial reported that zero out of 128 participants in the metformin group compared to four out of 120 participants in the comparator group experienced cardiovascular events (IDPP-1 2006).

Non-fatal stroke

No trial reported data exclusively on non-fatal stroke.

Amputation of lower extremity

None of the trials reported on amputation of lower extremity.

Blindness or severe vision loss

None of the trials reported on blindness or severe vision loss.

End-stage renal disease

None of the trials reported on end-stage renal disease

Non-serious adverse events

One trial reported on all non-serious adverse events (PREVENT-DM 2017). Ten (34.5%) out of 29 participants in the metformin group compared with zero out of 33 participants in the comparator group experienced a non-serious adverse event (PREVENT-DM

2017). Three trials reported on some adverse effects (DPP/DPPOS 2002; Fang 2004; IDPP-1 2006). In one trial, three out of 44 participants had diarrhoea in the metformin group compared to zero out of 36 participants in the comparator group (Fang 2004). One trial had two metformin groups (metformin monotherapy and metformin plus intensive diet and exercise), which were reported together. The trial reported that five out of 248 participants in the combined metformin groups experienced gastrointestinal symptoms compared to zero out of 120 participants in the comparator group (IDPP-1 2006). In one trial, 20 events of musculoskeletal symptoms per 100 person years and 78 events of gastrointestinal symptoms per 100 person years were experienced in the metformin group compared with 24 events of musculoskeletal symptoms per 100 person years and 13 events of gastrointestinal symptoms per 100 person years in the comparator group (DPP/DPPOS 2002).

Hypoglycaemia

One trial reported data on hypoglycaemia (IDPP-1 2006). In the two metformin groups (metformin monotherapy and metformin plus intensive diet and exercise), 22 out of 248 participants reported symptoms of mild hypoglycaemia; it was not possible to separate these data. No participant experienced symptoms of hypoglycaemia in the intensive diet plus exercise group (IDPP-1 2006).

Health-related quality of life

The DPP trial applied the SF-36 to evaluate the health utility index (SF-6D), physical component summaries (PCS) and mental component summaries (MCS). Minimal important difference (MID) was defined as scores between groups of at least 3% (DPP/DPPOS 2002). After a mean of 3.2 years of follow-up trial authors only reported the comparison metformin versus placebo, not metformin versus diet plus exercise (DPP/DPPOS 2002).

Time to progression to T2DM

After a median of 10 years follow-up in the DPP trial, the onset of diagnosis of T2DM was delayed by two years with metformin and four years with intensive diet and exercise compared with placebo (DPP/DPPOS 2002).

Measures of blood glucose control

2-hour glucose

Five trials reported data on 2-hour glucose (DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Li 2009): MD -0.03 mmol/L, 95% CI -0.26 to 0.20; P = 0.81; 2417 participants; 5 trials; Analysis 2.5.

Subgroup analysis: analysing trials according to blinded versus open-label trials could not be performed as all participants were aware of randomising to intensive diet plus exercise. Subgroup analysis according to duration of the intervention could not be performed as all trials reporting this outcome had a duration of intervention of two years or more. Subgroup analysis according to ethnicity did not show interaction between subgroups (P = 0.06; Analysis 2.6). Subgroup analysis according to diagnostic criteria, age, gender, comorbid condition and previous gestational diabetes could not be performed.

Sensitivity analysis: sensitivity analysis according to publication status could not be performed as all included trials were published. Sensitivity analysis restricted to only trials with low risk of selection

bias changed the direction of the effect estimate: MD 0.20 mmol/L, 95% CI 0.02 to 0.38; P = 0.03; 1834 participants; 1 trial (DPP/DPPOS 2002). Three trials were only published in Chinese. Sensitivity analysis restricted to trials published in English changed the direction of the effect estimate favouring intensive diet plus exercise: MD 0.20 mmol/L, 95% CI 0.02 to 0.37; P = 0.03; 2065 participants; 2 trials (DPP/DPPOS 2002; IDPP-1 2006). Sensitivity analysis excluding trials funded by a pharmaceutical company did not change the direction of the effect estimate: MD -0.32, 95% CI -0.83 to 0.19; P = 0.22; 352 participants; 3 trials (Fang 2004; Ji 2011; Li 2009).

HbA1c

Four trials reported data on HbA1c (Alfawaz 2018; DPP/DPPOS 2002; Ji 2011; PREVENT-DM 2017): MD 0.01% mmol/L, 95% CI -0.12 to 0.14; P = 0.93; 2135 participants; 4 trials; Analysis 2.7.

Subgroup analysis: analysing trials according to blinded versus open-label trials could not be performed as all participants were aware of randomising to intensive diet plus exercise. Subgroup analysis according to duration of the intervention did not show interaction between subgroups (P = 0.65; Analysis 2.8). Subgroup analysis according to ethnicity showed interaction between subgroups (P = 0.04; Analysis 2.9). Subgroup analysis according to diagnostic criteria, age, gender, comorbid condition and previous gestational diabetes could not be performed.

Sensitivity analysis: sensitivity analysis according to publication status could not be performed as all included trials were published. Sensitivity analysis restricted to only trials with low risk of selection bias did not substantially change the direction of the effect estimate: MD 0.00%, 95% CI -0.04 to 0.04; P = 1.0; 1834 participants; 1 trial (DPP/DPPOS 2002). One trial was only published in Chinese. Sensitivity analysis restricted to trials published in English did not change the direction of the effect estimate: MD 0.01%, 95% CI -0.13 to 0.16; P = 0.87; 2023 participants; 3 trials (Alfawaz 2018; DPP/DPPOS 2002; PREVENT-DM 2017). Sensitivity analysis excluding trials funded by a pharmaceutical company did not change the direction of the effect estimate: MD -0.10%, 95% CI -0.44 to 0.25; P = 0.59; 301 participants; 3 trials (Alfawaz 2018; Ji 2011; PREVENT-DM 2017).

Fasting plasma glucose

Seven trials reported data on fasting plasma glucose (Alfawaz 2018; DPP/DPPOS 2002; Fang 2004; IDPP-1 2006; Ji 2011; Li 2009; PREVENT-DM 2017). The MD was -0.26 mmol/L, 95% CI -0.59 to 0.07; P = 0.12; 2603 participants; 7 trials; Analysis 2.10.

Subgroup analysis: analysing trials according to blinded versus open-label trials could not be performed as all participants were aware of randomising to intensive diet plus exercise. Subgroup analysis according to duration of the intervention did not show interaction between subgroups (P = 0.09; Analysis 2.11). Subgroup analysis according to ethnicity did not show interaction between subgroups (P = 0.10; Analysis 2.12). Subgroup analysis according to diagnostic criteria, age, gender, comorbid condition and previous gestational diabetes could not be performed.

Sensitivity analysis: sensitivity analysis according to publication status could not be performed as all included trials were published. Sensitivity analysis restricted to only trials with low risk of selection bias changed the direction of the effect estimate: MD 0.00 mmol/L,

95% CI -0.07 to 0.07; $P = 1.0$; 1831 participants; 1 trial (DPP/DPPOS 2002). Three trials were only published in Chinese. Sensitivity analysis restricted to trials published in English changed the direction of the effect estimate: MD 0.0 mmol/L, 95% CI -0.07 to 0.07; $P = 0.95$; 2251 participants; 4 trials (Alfawaz 2018; DPP/DPPOS 2002; IDPP-1 2006; PREVENT-DM 2017). Sensitivity analysis excluding trials funded by a pharmaceutical company changed the direction of the effect estimate towards benefit of metformin: MD -0.37 mmol/L, 95% CI -0.65 to -0.09; $P = 0.009$; 541 participants; 5 trials (Alfawaz 2018; Fang 2004; Ji 2011; Li 2009; PREVENT-DM 2017).

Socioeconomic effects

Direct medical costs of the interventions during the DPP were estimated to be \$1177 for the metformin intervention versus \$3628 for the intensive diet plus physical activity group (DPP/DPPOS 2002). By year 10, the direct medical costs of the interventions and non-intervention-related medical costs were lower for the metformin group than for the intensive diet plus physical activity group (\$27,915 versus \$29,164).

The IDPP estimated direct medical costs of interventions over the 3-year trial period to be \$220 per participant in the metformin group compared with \$225 in the intensive diet and physical activity group (IDPP-1 2006).

Metformin versus insulin secretagogues

One trial compared metformin with a sulphonylurea (Papoz 1978). Metformin was administered in doses of 1700 mg/day with concomitant placebo. Glibenclamide was administered in doses of 4 mg/day with concomitant placebo. For both groups, overweight participants were recommended calorie restriction. The ethnicity of the included participants was not reported.

The trial reported 2-hour blood glucose and fasting blood glucose in mg/100 mL. The results were converted to plasma glucose measured in mmol/L and standard errors were converted to standard deviations (SDs). For the metformin group the 2-hour plasma glucose at the end of intervention was 7.2 mmol/L (SD 1.3) measured in 23 participants compared to 7.1 mmol/L (SD 1.3) measured in 22 participants in the glibenclamide group. For the metformin group the fasting plasma glucose at the end of intervention was 5.9 mmol/L (SD 0.5) measured in 23 participants compared to 5.6 mmol/L (SD 0.6) measured in 22 participants in the glibenclamide group.

Metformin versus acarbose

Three trials compared metformin with acarbose (Fang 2004; Liao 2012; Maji 2005). Several differences existed between these three trials. Two trials did not specify the concomitant intervention with diet and physical activity (Fang 2004; Liao 2012); the other trial specified that diet and physical activity was provided in both the metformin and the acarbose intervention groups (Maji 2005). Two trials included people with Chinese ethnicity (Fang 2004; Liao 2012), one trial included people with Indian ethnicity (Maji 2005). One trial administered metformin in doses up to 500 mg/day and acarbose in doses up to 50 mg/day (Maji 2005). One trial administered metformin in doses up to 1500 mg/day and acarbose in doses up to 300 mg/day (Liao 2012). One trial administered metformin in doses up to 2250 mg/day and acarbose in doses up to 450 mg/day (Fang 2004).

Primary outcomes

All-cause mortality

One trial reported data on all-cause mortality (Fang 2004). One participant out of 44 in the metformin group compared with zero out of 45 in the acarbose group died (Fang 2004).

Incidence of type 2 diabetes (T2DM)

All included trials reported data on the incidence of T2DM. A total of 12 out of 147 participants developed T2DM in the metformin group versus seven out of 148 participants in the comparator group (RR 1.72; 95% CI 0.72 to 4.14; $P = 0.22$; 295 participants; 3 trials; low-quality evidence; Analysis 4.2). Calculation of a 95% prediction interval was not meaningful.

Serious adverse events

In one trial one out of 51 participants in the metformin group experienced cerebral haemorrhage, whereas two out of 50 participants in the acarbose group experienced lung cancer and hepatitis, respectively (Liao 2012).

Secondary outcomes

Cardiovascular mortality

None of the trials reported on cardiovascular mortality.

Non-fatal myocardial infarction

None of the trials reported on non-fatal myocardial infarction.

Non-fatal stroke

None of the trials reported on non-fatal stroke.

Amputation of lower extremity

None of the trials reported on amputation of lower extremity.

Blindness or severe vision loss

None of the trials reported on blindness or severe vision loss.

End-stage renal disease

None of the trials reported on end-stage renal disease

Non-serious adverse events

One trial reported that in the metformin group three out of 44 participants experienced diarrhoea (Fang 2004). In the acarbose group one out of 45 participants experienced rash and one out of 45 participants experienced frequent venting (Fang 2004).

Hypoglycaemia

None of the trials reported on hypoglycaemia.

Health-related quality of life

None of the trials reported on health-related quality of life.

Time to progression to T2DM

None of the trials reported on time to progression to T2DM.

Measures of blood glucose control

2-hour glucose

Both included trials reported data on 2-hour glucose. Effects of intervention showed benefit in favour of acarbose: MD 0.49 mmol/L, 95% CI 0.09 to 0.88; $P = 0.02$; 190 participants; 2 trials; [Analysis 4.3](#).

One trial reported a mean 2-hour glucose of 5.9 mmol/L (SD 0.9) in the metformin group (unknown how many of the 48 initially randomised participants were included in the analysis) compared with 6.0 mmol/L (SD 0.5) in the acarbose group (unknown how many of the 48 initially randomised participants were included in the analysis) ([Maji 2005](#)).

HbA1c

One trial reported a mean HbA1c of 6.96% (SD 0.43) in the metformin group (unknown how many of the 48 initially randomised participants were included in the analysis) compared with 6.96% (SD 0.16) in the acarbose group (unknown how many of the 48 initially randomised participants were included in the analysis) ([Maji 2005](#)).

Fasting plasma glucose

Both included trials reported data on fasting plasma glucose. The MD was 0.00 mmol/L, 95% CI -0.35 to 0.35; $P = 0.99$; 190 participants; 2 trials; [Analysis 4.4](#).

One trial reported a mean fasting plasma glucose of 5.4 mmol/L (SD 0.3) in the metformin group (unknown how many of the 48 initially randomised participants were included in the analysis) compared with 5.5 mmol/L (SD 0.4) in the acarbose group (unknown how many of the 48 initially randomised participants were included in the analysis) ([Maji 2005](#)).

Socioeconomic effects

None of the trials reported on socioeconomic effects.

Metformin versus thiazolidinediones

Three trials compared metformin with a thiazolidinediones ([Jin 2009](#); [Maji 2005](#); [Zeng 2013](#)). One trial administered metformin in doses up to 38 mg/day and pioglitazone in doses up to 38 mg/day ([Zeng 2013](#)); one trial administered metformin in doses up to 500 mg/day and rosiglitazone in doses up to 2 mg/day ([Maji 2005](#)); and one trial administered metformin in doses up to 3000 mg/day and rosiglitazone in doses up to 4 mg/day ([Jin 2009](#)). All trials stated that both the intervention and comparator group received diet and exercise. Two trials included people with Chinese ethnicity ([Jin 2009](#); [Zeng 2013](#)), and one trial included people with Indian ethnicity ([Maji 2005](#)).

Primary outcomes

All-cause mortality

None of the trials reported on all-cause mortality..

Incidence of type 2 diabetes (T2DM)

All included trials reported data on incidence of T2DM. A total of nine out of 161 participants developed T2DM in the metformin group versus nine out of 159 participants in the comparator group (RR 0.99, 95% CI 0.41 to 2.40; $P = 0.98$; 320 participants; 3 trials; low-quality evidence; [Analysis 5.1](#)). Calculation of a 95% prediction interval was not meaningful.

Serious adverse events

In one trial, three out of 45 participants in the metformin group experienced severe gastrointestinal reactions and no serious adverse events were reported in the 41 participants in the thiazolidinedione group ([Jin 2009](#)).

Secondary outcomes

Cardiovascular mortality

None of the trials reported on cardiovascular mortality.

Non-fatal myocardial infarction

None of the trials reported on non-fatal myocardial infarction.

Non-fatal stroke

None of the trials reported on non-fatal stroke.

Amputation of lower extremity

None of the trials reported on amputation of lower extremity.

Blindness or severe vision loss

None of the trials reported on blindness or severe vision loss.

End-stage renal disease

None of the trials reported on end-stage renal disease.

Non-serious adverse events

One trial reported that in the rosiglitazone group one out of 41 participants experienced facial oedema and two out of 41 participants experienced intolerance of both lower limbs ([Jin 2009](#)).

Hypoglycaemia

One trial reported that no participant in any of the treatment arms experienced hypoglycaemia ([Jin 2009](#)).

Health-related quality of life

None of the trials reported on health-related quality of life.

Time to progression to T2DM

None of the trials reported on time to progression to T2DM.

Measures of blood glucose control

2-hour glucose

All included trials reported on 2-hour glucose. The MD was -0.54 mmol/L, 95% CI -1.80 to 0.73; $P = 0.41$; 224 participants; 2 trials; [Analysis 5.2](#).

One trial reported a mean 2-hour plasma glucose of 5.9 mmol/L (SD 0.9) in the metformin group (unknown how many of the 48 initially randomised participants were included in the analysis) compared with 5.8 mmol/L (SD 0.5) in the rosiglitazone group (unknown how many of the 48 initially randomised participants were included in the analysis) ([Maji 2005](#)).

HbA1c

One trial reported a mean HbA1c of 6.96% (SD 0.43) in the metformin group (unknown how many of the 48 initially randomised participants were included in the analysis) compared with 6.96% (SD 0.48) in the rosiglitazone group (unknown how

many of the 48 initially randomised participants were included in the analysis) (Maji 2005).

Fasting plasma glucose

All included trials reported on fasting plasma glucose. The MD was -0.13 mmol/L, 95% CI -0.32 to 0.07; $P = 0.20$; 224 participants; 2 trials; Analysis 5.3.

One trial reported a mean fasting plasma glucose of 5.4 mmol/L (SD 0.3) in the metformin group (unknown how many of the 48 initially randomised participants were included in the analysis) compared with 5.2 mmol/L (SD 0.4) in the rosiglitazone group (unknown how many of the 48 initially randomised participants were included in the analysis) (Maji 2005).

Socioeconomic effects

None of the trials reported on socioeconomic effects.

Metformin plus intensive diet and exercise versus intensive diet and exercise

Three trials compared metformin plus intensive diet and exercise with identical intensive diet and exercise (IDPP-1 2006; Iqbal Hydrie 2012; Zhao 2013). All the trials administered metformin in doses up to 1000 mg/day. The ethnicity of the included people were Indian (IDPP-1 2006), Pakistani (Iqbal Hydrie 2012), and Chinese (Zhao 2013).

Primary outcomes

All-cause mortality

IDPP-1 2006 reported that one out of 121 participants died in the metformin group compared to one out of 120 participants in the comparator group (very low-quality evidence). Iqbal Hydrie 2012 trial reported that zero out of 95 participants died in the metformin group compared with zero out of 114 participants in the comparator group (Analysis 6.1).

Incidence of type 2 diabetes (T2DM)

Two trials reported incidence of T2DM (IDPP-1 2006; Zhao 2013). A total of 48 out of 166 participants developed T2DM in the metformin plus intensive diet and exercise compared with 53 out of 166 participants in the comparator group (RR 0.55, 95% CI 0.10 to 2.92; $P = 0.49$; 332 participants; 2 trials; very low-quality evidence; Analysis 6.2). Calculation of a 95% prediction interval was not meaningful.

Serious adverse events

None of the trials reported on serious adverse events. All included trials had a high risk of selective reporting bias regarding serious adverse events.

Secondary outcomes

Cardiovascular mortality

One trial reported that no participant died due to cardiovascular causes (IDPP-1 2006).

Non-fatal myocardial infarction

None of the trials reported on non-fatal myocardial infarction.

Non-fatal stroke

None of the trials reported on non-fatal stroke.

Amputation of lower extremity

None of the trials reported on amputation of lower extremity.

Blindness or severe vision loss

None of the trials reported on blindness or severe vision loss.

End-stage renal disease

None of the trials reported on end-stage renal disease.

Non-serious adverse events

One trial had two metformin groups (metformin monotherapy and metformin plus intensive diet and exercise) and reported that five out of 248 participants in both metformin groups experienced gastrointestinal symptoms compared to zero out of 120 participants in the comparator group (IDPP-1 2006). One trial reported that one out of 45 participants in the metformin group experienced gastrointestinal symptoms compared with zero out of 46 participants in the comparator group (Zhao 2013).

Hypoglycaemia

One trial reported data on hypoglycaemia (IDPP-1 2006). In the two metformin groups (metformin monotherapy and metformin plus intensive diet and exercise), 22 out of 248 participants reported symptoms of mild hypoglycaemia; it was not possible to separate these data. None experienced symptoms of hypoglycaemia in the intensive diet plus exercise group (IDPP-1 2006).

Health-related quality of life

None of the trials reported on health-related quality of life.

Time to progression to T2DM

None of the trials reported on time to progression to T2DM.

Measures of blood glucose control

2-hour glucose

Two included trials reported on 2-hour glucose (IDPP-1 2006; Zhao 2013). The MD was -0.52 mmol/L, 95% CI -2.08 to 1.04; $P = 0.51$; 316 participants; 2 trials; Analysis 6.6).

HbA1c

None of the trials reported on HbA1c.

Fasting plasma glucose

Two trials reported data on fasting plasma glucose (IDPP-1 2006; Zhao 2013). The MD was -0.26 mmol/L, 95% CI -0.94 to 0.43; $P = 0.46$; 316 participants; 2 trials; Analysis 6.7.

Socioeconomic effects

The IDPP estimated direct medical costs of interventions over the three-year trial period to be \$270 per participant in the metformin plus intensive diet and physical activity group compared with \$225 in the intensive diet and physical activity group (IDPP-1 2006).

Ongoing trials

We identified 11 ongoing trials which potentially could provide data of interest for this review (CTRI/2017/09/009635; JPRN-UMIN000018995; Nadeau 2014; NCT01804049; Espinoza 2019;

NCT02915198; NCT02969798; Rhee 2019; NCT03194009; ePRECIDE 2017; Ji 2019). The trials will enrol a total of 17,853 participants. All but three ongoing trials explicitly stated that they assessed one or more of the primary or secondary outcomes of interest of this review (NCT01804049; Espinoza 2019; ePRECIDE 2017). Although not stated in the protocol, it is very likely that the remaining trials will assess one or more outcomes of interest for this review. Two trials did not report the trial completion date (CTRI/2017/09/009635; JPRN-UMIN000018995). One trial stated the trial completion date to be August 2018, but no trial results are available (NCT01804049). Two trials estimated the completion date to be in the year 2019 (Nadeau 2014; ePRECIDE 2017); two trials estimated the completion date to be in the year 2020 (NCT02969798; Rhee 2019); three trials estimated the completion date to be in the year 2022 (Espinoza 2019; NCT03194009; Ji 2019); and one trial estimated the completion date to be in the year 2024 (NCT02915198).

Studies awaiting assessment

One trial was published as an abstract only; the trial concluded "No differences were seen in relative risk for diabetes by 6 years with acarbose (1.04, $P = 0.81$), Metformin (0.99, $P = 0.94$) or combination therapy (1.02, $P = 0.91$). In those with IGT at baseline, relative risk was reduced significantly with acarbose (0.66, $P = 0.046$) but not Metformin (1.09, $P = 0.70$) or combination therapy (0.72, $P = 0.27$)" (EDIT 1997). For one trial it is unclear if the trial could be included, the principal investigator was contacted and replied that the trial is neither finished nor published (NCT02409238). For two trials, it is unclear if the trials could be included: one trial we contacted the author but we did not receive a reply (ChiCTR-IPR-17012309), and for the other trial we could not contact the author due to lack of contact information (Polanco 2015).

DISCUSSION

Summary of main results

This Cochrane Review investigated the effects of metformin in people at increased risk of developing type 2 diabetes mellitus (T2DM). We included 20 trials with a total of 6774 participants. We judged all trials to be unclear or high risk of bias in one or more 'Risk of bias' domains. Metformin compared with placebo or diet and exercise reduced or delayed the risk of T2DM in people at increased risk for the development of T2DM (moderate-quality evidence). However, metformin compared to intensive diet and exercise did not reduce or delay the risk of T2DM (very low-quality evidence). Likewise, for the combination of metformin and intensive diet and exercise compared to intensive diet and exercise only neither showed an advantage or disadvantage regarding the development of T2DM. The reporting of the incidence of T2DM for the remaining comparisons were sparse. The reporting of mortality and macrovascular and microvascular complications were sparse for all comparisons. Socioeconomic effects showed that metformin was more expensive than no treatment, however, assessment of the costs was not identical in the included trials reporting this outcome. The data on health-related quality of life were sparse. When reported, no firm influence of metformin was found. The certainty of the evidence for these outcome measures was low or very low.

Overall completeness and applicability of evidence

The diagnosis of intermediate hyperglycaemia varied among the trials and some trials used a definition that may have included participants judged to be euglycaemic or having T2DM. Most of the trials applied the criteria established by the World Health Organization (WHO) or American Diabetes Association (ADA) (impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), or both) to define intermediate hyperglycaemia. One trial applied the definition established by the European Diabetes Epidemiology Study Group 1970 (Papoz 1978). One trial applied cut-off points not recommended by any medical association (Maji 2005). This trial defined IGT with 2-hour plasma glucose after an oral glucose tolerance test (OGTT) ≥ 6.1 mmol/L and < 11.1 mmol/L and fasting plasma glucose < 6.1 mmol/L (Maji 2005).

Not all ethnicities were represented in the included trials; most of the trials included participants from Asia. One trial included mainly White people (DPP/DPPOS 2002) and one trial included Hispanic people only (PREVENT-DM 2017). Two trials were performed in France, but did not report the ethnicity of the included people (BIGPRO1 2009; Papoz 1978).

Detailed information about the participants was lacking in most trials. The included trials applied different doses of metformin. A potential selection bias might exist as more healthy and motivated people may participate in a clinical trial. However, a Cochrane Review observed that clinical outcomes in people participating in randomised controlled trials (RCTs) are comparable to similar people outside trials (Vist 2008).

One of the included trials contributed with about 48% of the included participants (DPP/DPPOS 2002). Reporting of complications associated with T2DM during the intervention period was lacking.

The number of participants diagnosed with T2DM in the control groups of the included trials was higher than that estimated from observational trials (Cheng 2006; Morris 2013). This might be explained by the regular glycaemic testing of people participating in a RCT. Therefore, many of those diagnosed with T2DM in a RCT may not be diagnosed in a 'real-world' setting.

We conducted an extensive search for trials, including publication in all languages. In total, 11 trials were published in Chinese only. We tried to contact all authors to obtain additional data, however, only two authors replied (BIGPRO1 2009; DPP/DPPOS 2002). No additional data were provided. We looked for additional data and cross-checked our data with systematic reviews of relevance. Examination of four systematic reviews (Haw 2017; Lily 2009; Moelands 2018; Salpeter 2008) revealed three additional references. One systematic review (Pang 2018) revealed a further 10 Chinese trials to be included.

Quality of the evidence

None of the 20 included trials in our review was classified as having low risk of bias in all 'Risk of bias' domains. Only three out of 20 trials provided sufficient information on the method of randomisation and allocation concealment (Alfawaz 2018; DPP/DPPOS 2002; PREVENT-DM 2017). Four trials explicitly reported blinding of participants and investigators (BIGPRO1 2009; DPP/DPPOS 2002; Li 1999; Papoz 1978). In all the included trials the assessment of the primary outcomes of this review

and measurement of glucose values were performed by the investigators. We judged these outcomes as objective and unlikely to be influenced by lack of blinding. Only five trials provided sufficient information on incomplete outcome data (BIGPRO1 2009; DPP/DPPOS 2002; Ji 2011; Lu 2010; PREVENT-DM 2017). Most of the trials were judged to have high risk of selective outcome reporting because one or more outcomes of relevance for our review were likely assessed but not reported and/or the protocol could not be retrieved. Three of the included trials stated that they had received funding from a pharmaceutical company (BIGPRO1 2009; DPP/DPPOS 2002; IDPP-1 2006). It is known that trials receiving funding or provision of free drug or devices from a pharmaceutical company leads to more favourable results and conclusions than trials sponsored by other sources (Lundh 2017).

For the comparisons 'metformin versus placebo or diet and exercise' and 'metformin versus intensive diet plus exercise' outcomes were judged to be of very low, low or moderate quality of the evidence. For the remaining comparisons, outcomes were judged to be of very low- or low-quality evidence.

We included trials with an intervention duration of one year or more. Trials with shorter duration could have been included, but as we were focusing on patient-important outcomes we did not include such short-term trials.

Potential biases in the review process

Many of the included trials were not designed or powered to detect our predefined patient-important outcomes. For the performed meta-analyses we investigated heterogeneity and the potential reasons for it through subgroup and sensitivity analyses. We were dealing with a substantially heterogeneous group of trials. Our meta-analyses were limited by the inability to use individual participant data to assess whether distinct clinical characteristics may have influenced the effect estimates of the interventions. We tried to contact all trial authors for clarification if one of the bias domains was not adequately reported, however, most of the authors did not reply. We included trials with a minimum duration of one year in order to detect clinically relevant differences for the predefined outcomes. Even though we focused on long-term trials, the reporting of clinical outcomes in the included trials was sparse. Two review authors carried out data extraction. However, the review authors extracting the data were not blinded as to which trial they were extracting data from.

Agreements and disagreements with other studies or reviews

Recently, several systematic reviews (Haw 2017; Lily 2009; Moelands 2018; Pang 2018; Salpeter 2008) have investigated strategies to prevent or delay T2DM in people at increased risk of T2DM. However, only a few of the systematic reviews have focused on metformin for prevention of T2DM in people at risk for T2DM (Lily 2009; Salpeter 2008). Both of these publications performed a search with no language restriction. One systematic review included three RCT's with a follow-up time of at least six months investigating people with IGT or IFG (Lily 2009). This review only included trials that focused on the development of T2DM as the primary outcome and thus could have missed potential relevant data if incidence of T2DM was reported as a secondary or other outcome. The review found that metformin was effective in reducing the incidence of T2DM (fixed odds ratio (OR) 0.65, 95%

confidence interval (CI) 0.55 to 0.78). Another trial included 31 RCT's with a duration of at least eight weeks (Salpeter 2008). The review included trials with people at increased risk for T2DM defined as people with obesity, polycystic ovary syndrome (PCOS), insulin resistance, impaired glucose tolerance, family history of diabetes, peripheral vascular disease or metabolic syndrome. Due to the wide inclusion criteria, the review possibly included normoglycaemic people and is therefore difficult to compare with our review. Our search did not provide any other relevant systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-quality evidence that metformin compared with placebo or diet and exercise reduced or delayed the risk of type 2 diabetes mellitus (T2DM) in people with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). Following diet and exercise or a non-metformin antidiabetic drug 281 per 1000 participants developed T2DM compared with 141 per 1000 participants (95% confidence interval (CI) 107 to 183) after metformin therapy.

However, metformin compared to intensive diet and exercise did not reduce or delay the risk of T2DM (moderate-quality evidence). Following intensive diet and exercise 167 per 1000 participants developed T2DM compared with 133 per 1000 participants (95% CI 78 to 228) after metformin therapy.

Likewise, the combination of metformin and intensive diet and exercise compared to intensive diet and exercise only neither showed an advantage or disadvantage regarding the development of T2DM (very low-quality evidence). Following intensive diet and exercise 289 per 1000 participants developed T2DM compared with 159 per 1000 participants (CI 29 to 844) after metformin combined with intensive diet and exercise.

It needs to be clarified, whether there is the same metformin effect in people with increased risk defined by other glycaemic variables, such as elevated glycosylated haemoglobin A1c (HbA1c) levels.

Data on patient-important outcomes such as mortality, macrovascular and microvascular diabetic complications and health-related quality of life were sparse or missing.

Implications for research

It remains to be clarified whether the reduction or delay in the incidence of type 2 diabetes mellitus with metformin in people with IGT and/or IFG can decrease the long-term risk of complications associated with T2DM. Future trials should also investigate the effect of metformin in people with moderately elevated HbA1c and focus on patient-important outcomes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Alfawaz 2018

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1
Participants	<p>Inclusion criteria: fasting glucose level of 5.6 mmol/L to 6.9 mmol/L; the participants were identified through screening as recommended in guidelines by ADA 2017</p> <p>Exclusion criteria: receiving glucose-lowering intervention; pregnant or lactating women; renal, hepatic, pulmonary, cardiac complications</p> <p>Diagnostic criteria: ADA 2017 criteria for IFG (fasting glucose 5.6 mmol/L to 6.9 mmol/L)</p>
Interventions	<p>Number of study centres: 2</p> <p>Run-in period: none</p> <p>Administration-free period before testing during trial: not reported</p> <p>Extension period: none</p>
Outcomes	Composite outcome measures reported: metabolic syndrome (primary outcome)

Alfawaz 2018 (Continued)

Study details	Trial terminated early: no	
Publication details	Language of publication: English Funding: non-commercial funding Publication status: peer-reviewed journal	
Stated aim of study	Quote from publication: "... aimed to determine the differences in the effects of general advice (GA) on lifestyle change, intensive lifestyle modification programme (ILMP) and GA + metformin (GA + Met) in reducing the prevalence of full metabolic syndrome (MetS) in subjects with prediabetes"	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "A computer-generated serial number, randomly assigned..." Comment: adequate description of the sequence generation
Allocation concealment (selection bias)	Low risk	Quote from publication: "True allocation concealment was done since the research personnel involved cannot adjust randomization" Comment: adequate description of allocation concealment
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: investigator-assessed outcome measure, unclear if this outcome also was assessed by the blinded independent outcome committee. The outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: investigator-assessed outcome measure, unclear if this outcome also was assessed by the blinded independent outcome committee. The outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	Quote from publication: "Hence, the missing data (<5% of the total data points in any variable) was dealt with the last observation carried forward (LOCF) method. However, as much as possible, the LOCF was minimized by removing the data of the subjects lost to follow up at 6-month or 12-month and also by removing ones with >5% missing data in any variable" Comment: in metformin plus general advise on diet and exercise group 60.2% of randomised participants were analysed. In intensive lifestyle modification programme group and general advise on diet and exercise group 74.5% and 86.7% of randomised participants were analysed, respectively. Drop-out rates were not balanced (69.4 to 95.9% of randomised participants finished the trial). Reasons for drop-outs were not balanced. Plausible effect size among missing outcomes enough to induce clinically-relevant bias in observed effect size
Selective reporting (reporting bias)	High risk	Comment: no trial protocol available. Likely that the incidence of T2DM as well as adverse events has been collected during the trial, but not reported
Other bias	Low risk	Comment: the trial appeared to be free of other sources of bias

BIGPRO1 2009

Methods	Parallel randomised controlled trial, randomisation ratio 1:1	
Participants	<p>Inclusion criteria: participants with a high waist-to-hip ratio (≥ 0.95 in men; ≥ 0.80 in women), who were considered to be non-diabetic. Other trial inclusion criteria were age (35 to 60 years for men, 40 to 65 years for women), absence of cardiovascular diseases and no contraindications to the use of metformin</p> <p>Exclusion criteria: participants with Ischaemic cardiovascular disease, diabetes, psychiatric disorders, heavy chronic medical treatment, serious life-threatening medical conditions, impaired renal function and lactic acidosis were excluded</p> <p>Diagnostic criteria: WHO 1999 (IFG is defined as a FPG of 110 mg/dL to 125 mg/dL (6.1 mmol/L to 6.9 mmol/L) and IGT as a 2hPG of 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L))</p>	
Interventions	<p>Number of study centres: 33</p> <p>Run-in period: none</p> <p>Administration-free period before testing during trial: NR</p> <p>Extension period: no</p>	
Outcomes	Composite outcome measures reported: no	
Study details	Trial terminated early: no	
Publication details	<p>Language of publication: English</p> <p>Funding: both commercial funding (Lipha Pharmaceuticals Ltd) and non-commercial funding (INSERM, CNAMts)</p> <p>Publication status: peer-reviewed journal</p>	
Stated aim of study	Quote from publication: "To study the effects of 1 year of treatment with metformin versus placebo on the clinical and metabolic parameters described as part of the metabolic syndrome"	
Notes	<p>Data on the people with IFG and IGT were only a subset of participants 101 out of 457 (22.1%) and reported in a post hoc analysis.</p> <p>Quote from publication: "Analyses were performed in the subset of trial patients who had impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), or both, according to the 1999 WHO definition [13], wherein IFG is defined as a FPG of 110–125 mg/dL (6.1–6.9 mmol/L) and IGT as a 2hPG of 140–199 mg/dL (7.8–11.0 mmol/L). In addition, these analyses were repeated in another subset of subjects, defined according to inclusion criteria of the DPP [5]—namely, body mass index (BMI)≥ 24 kg/m², FPG of 95–125 mg/dL (5.3–6.9 mmol/L) and 2hPG of 140–199 mg/dL (7.8–11.0 mmol/L)."</p> <p>"Of the 457 subjects included in the BIGPRO1 trial, 101 (22%; 49 in the metformin group and 52 in the placebo group) had IFG or IGT at baseline, with eight subjects in the metformin group and 11 in the placebo group having isolated IFG; and 51 (11%; 28 in the metformin group and 23 in the placebo group) met the DPP inclusion criteria."</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "Confidential balanced random lists are used to allocate to every patient's number metformin or placebo,..."

BIGPRO1 2009 (Continued)

		Comment: adequate description of the sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Quote from publication: "..., in double-blind fashion, i.e. packages. are similar whatever their content and only identified by the patient' trial number."</p> <p>Comment: blinding of participants and key study personnel ensured</p>
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	<p>Quote from publication: "..., in double-blind fashion, i.e. packages. are similar whatever their content and only identified by the patient' trial number."</p> <p>Comment: blinding of investigators, who were outcome assessors are ensured</p>
Incomplete outcome data (attrition bias) all-cause mortality/cardiovascular mortality	Low risk	
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	<p>Quote from publication: "All patient who definitively stop the trial treatment for any reason continue to be followed up and examined a scheduled" and "At 12 months, 37 subjects (21 metformin, 16 placebo) in the IFG/IGT subset and 19 (10 metformin, 9 placebo) in the DPP subset had dropped out. The reasons for the subjects' absence at 12 months were roughly similar between treatment groups, with only a slight tendency to a greater influence of side effects in the metformin group and a lack of motivation in the placebo group. To assess whether this dropout rate had any effect on the initial comparability of the two treatment groups, baseline characteristics were compared between those who missed the last visit and the remaining subjects. The only difference found was that those remaining in the trial were more often treated for hypertension than the dropouts (45% and 16%, respectively, in the IFG/IGT subset, $P < 0.003$; 47% and 21%, respectively, in the DPP subset, $P = 0.07$)."</p> <p>Comment: it is predefined to include all randomised participants. In the post hoc analysis of the participants with IFG and/or IGT only 63% of the participants are included in the analyses. This might introduce clinical relevant bias in effect estimates.</p>
Selective reporting (reporting bias)	High risk	Comment: adverse events and incidence of T2DM were assessed in the total population, but not reported in the subset with IGT and/or IFG. However, these analyses were not predefined in the protocol.
Other bias	High risk	Comment: several authors have conflicts of interest, and the trial has received pharmaceutical funding

Chen 2009

Methods	Parallel randomised controlled trial, randomisation ratio 1:1
Participants	<p>Inclusion criteria: IGT</p> <p>Exclusion criteria: liver and kidney dysfunction</p> <p>Diagnostic criteria: WHO 1999 (2hPG of 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L))</p>

Chen 2009 (Continued)

Interventions	Number of trial centres: 1	
	Run-in period: not reported	
	Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of the intervention. However, for participants who did not convert to diabetes, the fasting and 2-hour 75g-OGTT blood glucose was detected at 1-year follow-up after drug withdrawal.	
	Extension period: none	
Outcomes	Composite outcome measures reported: none	
Study details	Trial terminated early: no	
Publication details	Language of publication: Chinese	
	Funding: not reported	
	Publication status: peer-reviewed journal, full article	
Stated aim of study	Quote from publication: "To observe the effect of Shenqi Jiangtang capsule on preventing type 2 diabetes in IGT patients."	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "randomised" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	Quote from publication: "A total of 17 patients withdrew during the observation period, including 6 in the Shenqi Jiangtang capsule group, 6 in the general life intervention group and 5 in the metformin group."

Chen 2009 (Continued)

		Comment: no reason given and PP analysis used (only reported)
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	Quote from publication: "A total of 17 patients withdrew during the observation period, including 6 in the Shenqi Jiangtang capsule group, 6 in the general life intervention group and 5 in the metformin group." Comment: no reason given and PP analysis used (only reported)
Selective reporting (reporting bias)	High risk	Comment: protocol unavailable, non-SAE likely to have been analysed but not reported. Outcomes stated in the methods were reported in the results (BMI, liver and kidney function)
Other bias	Unclear risk	Comment: unknown funding source

DPP/DPPOS 2002

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1
Participants	<p>Inclusion criteria: ≥ 25 years, BMI ≥ 24 kg/m² in Asians BMI ≥ 22 kg/m², FPG 95 mg/dL to 125 mg/dL (5.3 mmol/L to 6.9 mmol/L) and 2-hour OGTT 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L). Because of the relative higher rate of progression from IGT to diabetes in Native Americans and the small size of the population, the glucose requirement for eligibility in the Southwest American Indian Center will be fasting glucose < 126 mg/dL (7.0 mmol/L) and 2-hour plasma glucose 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L).</p> <p>Exclusion criteria: T2DM, participants taking medicines known to alter glucose tolerance, ever used glucose-lowering drugs during pregnancy, illnesses that could seriously reduce their life expectancy or their ability to participate in the trial, cardiovascular disease (hospitalisation for treatment of heart disease in past 6 months; NYHA class > 2; left bundle branch block or third degree atrioventricular block; aortic stenosis; SBP > 180 mmHg or DBP > 105 mmHg); cancer requiring treatment in the past five years (unless prognosis is considered good); renal disease; gastrointestinal disease; anaemia (haematocrit $< 36.0\%$ in men or $< 33.0\%$ in women); electrolyte abnormality (serum potassium < 3.2 or > 5.5 mmol/L).</p> <p>Diagnostic criteria: IGT (2-hour OGTT 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L)) and elevated fasting glucose (FPG 95 mg/dL to 125 mg/dL (5.3 mmol/L to 6.9 mmol/L)) (ADA 1997).</p>
Interventions	<p>Number of study centres: 27</p> <p>Treatment before study: none</p> <p>Run-in period: 3 weeks; during the run-in period the participants had to fill out a daily diary and placebo pills according to a schedule</p> <p>Extension period: yes, an additional follow-up with a median of 5.7 years (IQR 5.5 to 5.8) after end of the intervention period</p>
Outcomes	Composite outcome measures reported: yes (Quote from publication: "...a composite microvascular-neuropathic outcome for diabetic retinopathy, nephropathy, or reduced light touch sensation in the feet. Secondary outcomes include the individual components of the composite primary outcome, cardiovascular disease, further development of diabetes, measures of glycaemia, insulin secretion, insulin sensitivity, cardiovascular disease risk factors, physical activity, nutrition, bodyweight, health-related quality of life, and economic assessments.")
Study details	Trial terminated before regular end (for benefit/because of adverse events): the trial was stopped one year earlier than originally planned due to larger intervention effect of diet and physical activity than anticipated.

DPP/DPPOS 2002 (Continued)

Taking trial drug on glycaemic testing days: placebo and metformin was not taken on the morning of glycaemic testing

Publication details

Language of publication: English

Funding: commercial funding (Lipha (Merck-Sante) provided medicines, and LifeScan donated materials) / non-commercial funding (the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Child Health and Human Development, the National Institute on Aging, the National Eye Institute, the National Heart Lung and Blood Institute, the Office of Women's Health, the National Center for Minority Health and Human Disease, the Centers for Disease Control and Prevention, and the American Diabetes Association)

Publication status: peer-reviewed journal

Stated aim of study

Quote from publication: "The principal objective of the DPP is to prevent or delay the development of NIDDM in those persons who are at high risk for its development by virtue of having impaired glucose tolerance"

Notes

Individuals who meet only one of the glucose inclusion criteria was rescreened after 6 months.

Because of the relative higher rate of progression from IGT to T2DM in Native Americans and the small size of the population, the glucose requirement for eligibility in the Southwest American Indian Center differed (see above).

The trial included initially four intervention groups. The troglitazone group was discontinued in 1998 because of potential liver toxicity.

Risk of bias

Bias

Authors' judgement

Support for judgement

Random sequence generation (selection bias)

Low risk

Quote from publication: "A sequence of randomization numbers within a clinical center will be constructed of the form XXYZZZ, where XX is the clinical center number, Y is a number that indicates assignment to either the intensive lifestyle intervention or pharmacological treatment, and ZZZ is a three digit sequence number within each XXY combination. The DPP Coordinating Center will prepare the master randomization list with assignments to the three treatment groups within a clinical center using the standard urn design. The sequence of pharmacological randomization numbers within a clinical center with the specific pharmacological treatment assignment (i.e., metformin or placebo) will be forwarded, in confidence, to the drug distribution center for drug labelling and distribution. Pharmacological treatment assignment to the sequence of pharmacological randomization numbers will be known only by the staff of the DPP Coordinating Center and the drug distribution center."

Comment: adequate description of the sequence generation

Allocation concealment (selection bias)

Low risk

Quote from publication: "A sequence of randomization numbers within a clinical center will be constructed of the form XXYZZZ, where XX is the clinical center number, Y is a number that indicates assignment to either the intensive lifestyle intervention or pharmacological treatment, and ZZZ is a three digit sequence number within each XXY combination. The DPP Coordinating Center will prepare the master randomization list with assignments to the three treatment groups within a clinical center using the standard urn design. The sequence of pharmacological randomization numbers within a clinical center with the specific pharmacological treatment assignment (i.e., metformin or placebo) will be forwarded, in confidence, to the drug distribution center for drug labeling and distribution. Pharmacological treatment assignment to the sequence of pharmacological randomization numbers will be

DPP/DPPOS 2002 (Continued)

		known only by the staff of the DPP Coordinating Center and the drug distribution center."
		Comment: adequate allocation concealment ensured
Blinding of participants and personnel (performance bias) all-cause mortality/cardiovascular mortality	Low risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded."</p> <p>Comment: no blinding for the comparison of metformin with intensive diet and physical activity, but judged that the outcome is not likely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded." and "Primary outcome data (OGTT and FPG results) measured centrally will remain masked to the investigators and to the participants until confirmed progression from IGT to diabetes"</p> <p>Comment: assessed centrally unblinded, the outcome is not likely to be influenced by lack of blinding. Participants and investigators blinded to until progression to T2DM</p>
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded." and "Primary outcome data (OGTT and FPG results) measured centrally will remain masked to the investigators and to the participants until confirmed progression from IGT to diabetes" and Plasma lipid levels and HbA1c measured centrally will remain masked to the investigators and to the participants during the study."</p> <p>Comment: assessed centrally unblinded, the outcome is not likely to be influenced by lack of blinding. Participants and investigators blinded to until progression to T2DM</p>
Blinding of participants and personnel (performance bias) socioeconomic effects	Low risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded."</p> <p>Comment: no blinding for the comparison of metformin with intensive diet and physical activity, but judged that the outcome is not likely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) health-related quality of life	High risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded."</p> <p>Comment: no blinding for the comparison of metformin with intensive diet and physical activity and the outcome is likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded." and "Primary outcome data (OGTT and FPG results) measured centrally will remain masked to the investigators and to the participants until confirmed progression from IGT to diabetes"</p>

DPP/DPPOS 2002 (Continued)

		<p>Comment: assessed centrally unblinded, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded." and "Primary outcome data (OGTT and FPG results) measured centrally will remain masked to the investigators and to the participants until confirmed progression from IGT to diabetes" and "Plasma lipid levels and HbA1c measured centrally will remain masked to the investigators and to the participants during the study."</p> <p>Comment: assessed centrally unblinded, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) socioeconomic effects	Low risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded."</p> <p>Comment: no blinding for the comparison of metformin with intensive diet and physical activity but judged that the outcome is not likely to be influenced by lack of blinding, investigator-assessed outcome measurement</p>
Blinding of outcome assessment (detection bias) health-related quality of life	High risk	<p>Quote from publication: "Masking intensive lifestyle intervention assignment to the participants is not possible and masking the investigators is not practical." and "Assignments to metformin and placebo were double-blinded."</p> <p>Comment: no blinding for the comparison of metformin with intensive diet and physical activity and the outcome is likely to be influenced by lack of blinding, self-reported outcome measurement</p>
Incomplete outcome data (attrition bias) all-cause mortality/cardiovascular mortality	Low risk	<p>Quote from publication: "At the close of the study, 99.6 percent of the participants were alive, of whom 92.5 percent had attended a scheduled visit within the previous five months"</p> <p>Comment: not stated how many participants who had known vital status in each intervention group at the end of follow-up for the DPP trial. However, at inception of the number with unknown mortality status are relatively low. At inception of the DPPOS the number between the intervention groups we balanced.</p>
Incomplete outcome data (attrition bias) incidence of T2DM	Low risk	<p>Quote from publication: "At the close of the study, 99.6 percent of the participants were alive, of whom 92.5 percent had attended a scheduled visit within the previous five months"</p> <p>Comment: not stated how many participants who had known vital status at the end of follow-up for the DPP trial. However, at inception of the DPPOS a relatively low and balanced number of participants in the intervention groups could not be included.</p>
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	<p>Comment: not stated how many participants who had known vital status at the end of follow-up for the DPP trial. However, at inception of the DPPOS a relatively low and balanced number between the intervention groups could not be included.</p>
Incomplete outcome data (attrition bias) time to progression to T2DM	Low risk	<p>Comment: "At the close of the study, 99.6 percent of the participants were alive, of whom 92.5 percent had attended a scheduled visit within the previous five months"</p>

DPP/DPPOS 2002 (Continued)

Incomplete outcome data (attrition bias) socioeconomic effects	Low risk	Comment: not clearly described how many participants included in the costs analyses, but as the study have a high follow-up rate, we assume that nearly all participants are included.
Incomplete outcome data (attrition bias) health-related quality of life	Low risk	Quote from publication: " the current reports and analyses includes 3,234 participants seen at baseline, who were randomly assigned to one of the three treatment arms investigated." Comment: article reporting health related quality of life do not report the number of participants with available data at follow-up
Selective reporting (reporting bias)	High risk	Comment: several outcome are likely to be measured and analysed, but not reported, e.g. hypoglycaemia, non-serious adverse events. Outcomes published in many different publications. Several outcomes are reported incompletely so that they cannot be included in meta-analysis
Other bias	Unclear risk	Comment: received funding from a pharmaceutical company

Fang 2004

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1:1
Participants	Inclusion criteria: participants in accordance with the diagnostic criteria of IGT Exclusion criteria: participants with severe somatological disease, mental disease or history of mental disease, severe intellectual or cognitive disorders, drug or alcohol dependence Diagnostic criteria: IGT
Interventions	Number of study centres: 1 Run-in period: not described Administration-free period before testing during trial: not reported Extension period: none
Outcomes	Composite outcome measures reported: none
Study details	Trial terminated before regular end (for benefit/because of adverse events): no Taking trial drug on glycaemic testing days: not specified if any study drug was taken on the testing day at the end of the intervention.
Publication details	Language of publication: Chinese Funding: not described Publication status: full article (Chinese Journal of Clinical Rehabilitation)
Stated aim of study	Quote from publication: "To observe influence of medicine intervention and non-medicine intervention on the outcomes of the crowd with IGT and explore which intervention can prevent IGT from developing to diabetes mellitus more effectively."
Notes	

Risk of bias

Fang 2004 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "Patients were randomly allocated by random number table." Comment: adequate description of the sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) all-cause mortality/cardiovascular mortality	Low risk	Comment: no description of blinding, but according to the intervention arms in the trial, neither the participants or the personnel were blinded. The outcome is not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no description of blinding, but according to the intervention arms in the trial, neither the participants or the personnel were blinded. The outcome is not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: no description of blinding, but according to the intervention arms in the trial, neither the participants or the personnel were blinded. The outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) all-cause mortality/cardiovascular mortality	Low risk	Comment: unclear whether outcome assessors were blinded, but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: unclear whether outcome assessors were blinded, but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: unclear whether outcome assessors were blinded, but the outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) all-cause mortality/cardiovascular mortality	Unclear risk	Quote from publication: "160/178 (90%) were analysed" Comment: unclear description on how missing data were handled
Incomplete outcome data (attrition bias) incidence of T2DM	Unclear risk	Quote from publication: "160/178 (90%) were analysed" Comment: unclear description on how missing data were handled
Incomplete outcome data (attrition bias) measures of blood glucose control	Unclear risk	Quote from publication: "160/178 (90%) were analysed" Comment: unclear description on how missing data were handled
Selective reporting (reporting bias)	Unclear risk	Comment: no trial protocol available

Fang 2004 (Continued)

Other bias	Unclear risk	Comment: unclear funding source
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IDPP-1 2006

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1:1
Participants	<p>Inclusion criteria: IGT (mean 2-hour plasma glucose after OGTT 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L) and FPG < 126 mg/dL (7.0 mmol/L)) (WHO 1999); no major illness; 35 to 55 years</p> <p>Exclusion criteria: diagnosis of T2DM during recruitment; pregnancy</p> <p>Diagnostic criteria: IGT (WHO 1999)</p>
Interventions	<p>Number of study centres: -</p> <p>Run-in period: none</p> <p>Administration-free period before testing during trial: not reported</p> <p>Titration period: none</p>
Outcomes	Composite outcome measures reported: yes (cardiovascular disease)
Study details	<p>Trial terminated before regular end (for benefit/because of adverse events): yes; Quote from publication: "After a median follow-up period of 30 months, because there were significant differences in the outcome measure between the control and intervention groups, the committee recommended the termination of the study in December 2004"</p> <p>Taking trial drug on glycaemic testing days: not specified</p>
Publication details	<p>Language of publication: English</p> <p>Funding: commercial (M/S US Vitamins)</p> <p>Publication status: peer-reviewed journal</p>
Stated aim of study	Quote from publication: "In a prospective community-based study, we tested whether the progression to diabetes could be influenced by interventions in native Asian Indians with IGT who were younger, leaner and more insulin resistant than the above populations"
Notes	Two more intervention groups existed that were not included in this review; 1) metformin and 2) diet plus physical activity combined with metformin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote from publication: "A randomised, controlled clinical trial was performed in subjects who were....."</p> <p>Comment: insufficient information about the sequence generation process</p>
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	Quote from publication: "Masking: Open Label" and "However, the principal investigators were blinded to the outcome until they were asked to close the study by the international data monitoring committee."

IDPP-1 2006 (Continued)

all-cause mortality/cardiovascular mortality		Comment: outcome evaluated by an independent outcome committee. Outcome unlikely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Quote from publication: "Masking: Open Label" "However, the principal investigators were blinded to the outcome until they were asked to close the study by the international data monitoring committee."</p> <p>Comment: outcome evaluated by an independent outcome committee and investigator-assessed outcome measure</p>
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Quote from publication: "Masking: Open Label" and ""However, the principal investigators were blinded to the outcome until they were asked to close the study by the international data monitoring committee."</p> <p>Comment: investigator-assessed outcome measure, unclear if this outcome also was assessed by the blinded independent outcome committee. The outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) all-cause mortality/cardiovascular mortality	Low risk	<p>Quote from publication: "However, the principal investigators were blinded to the outcome until they were asked to close the study by the international data monitoring committee."</p> <p>Comment: outcome evaluated by an independent outcome committee</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Quote from publication: "However, the principal investigators were blinded to the outcome until they were asked to close the study by the international data monitoring committee."</p> <p>Comment: outcome evaluated by an independent outcome committee and investigator-assessed outcome measure</p>
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	<p>Quote from publication: "However, the principal investigators were blinded to the outcome until they were asked to close the study by the international data monitoring committee."</p> <p>Comment: investigator-assessed outcome measure, unclear if this outcome also was assessed by the blinded independent outcome committee. The outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) non-serious adverse events	High risk	
Incomplete outcome data (attrition bias) all-cause mortality/cardiovascular mortality	Unclear risk	Comment: unknown whether mortality status was known on the participants lost to follow-up. The proportion of missing outcomes compared with observed event risk may have a clinically relevant impact on the intervention effect estimate
Incomplete outcome data (attrition bias) incidence of T2DM	Unclear risk	Comment: the proportion of missing outcomes compared with observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate
Incomplete outcome data (attrition bias) measures of blood glucose control	Unclear risk	Comment: Insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias
Selective reporting (reporting bias)	High risk	Quote from publication: "An internal safety committee monitored the adverse events and safety of study protocol. The data and final outcome mea-

IDPP-1 2006 (Continued)

tures were monitored by the international monitoring committee who had looked at the results three times, i.e. when 500 subjects had completed the follow-up assessments at 12, 24 and 30 months. The principal investigators were blinded to the interim results."

Comment: several outcomes with relevance for this review are not reported or only reported in a format which makes them unsuitable for meta-analyses, e.g. adverse events

Other bias	Unclear risk	Comment: role of funding source not described
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Iqbal Hydrie 2012

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1	
Participants	Inclusion criteria: IGT, > 30 years Exclusion criteria: NS Diagnostic criteria: WHO 1999 criteria (FPG < 7.0 mmol/L and 2-hour plasma glucose after OGTT \geq 7.8 mmol/L and < 11.1 mmol/L)	
Interventions	Number of study centres: multicentre, but number of centres not reported Run-in period: none Administration-free period before testing during trial: not reported Extension period: no	
Outcomes	Composite outcome measures reported: no	
Study details	Trial terminated before regular end (for benefit/because of adverse events): no Taking trial drug on glycaemic testing days: not specified	
Publication details	Language of publication: English Funding: non-commercial funding Publication status: peer-reviewed journal	
Stated aim of study	Quote from publication: "To observe the rate of conversion from impaired glucose tolerance (IGT) to diabetes following lifestyle modification (LSM) or a combination of lifestyle and metformin compared to a control population with 18-month followup"	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "After taking informed consent, the participants were randomized by age strata (31–40 years, 41–50 years, 51–60 years, and >60 years) into three different arms" Comment: insufficient information about the sequence generation

Iqbal Hydrie 2012 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) all-cause mortality/cardiovascular mortality	Low risk	Comment: no blinding, but the outcome is not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no blinding, but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) all-cause mortality/cardiovascular mortality	Low risk	Comment: no blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: no blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) all-cause mortality/cardiovascular mortality	Unclear risk	<p>Quote from publication: "Overall 44 subjects dropped out or were lost to followup. In the control group there were 2 deaths while 24 subjects dropped out during the study. In the lifestyle modification group 8 subjects refused to continue the study and dropped out. In the LSM + drug group 5 subjects stopped taking the drug either due to side effects of the drug such as gastrointestinal problems or complaining of weakness probably due to hypoglycemia while 5 subjects refused to follow due to personal reasons and were lost to followup."</p> <p>Comment: unknown whether mortality status was investigated in the people lost to follow-up</p>
Incomplete outcome data (attrition bias) incidence of T2DM	Unclear risk	<p>Quote from publication: "Overall 44 subjects dropped out or were lost to followup. In the control group there were 2 deaths while 24 subjects dropped out during the study. In the lifestyle modification group 8 subjects refused to continue the study and dropped out. In the LSM + drug group 5 subjects stopped taking the drug either due to side effects of the drug such as gastrointestinal problems or complaining of weakness probably due to hypoglycemia while 5 subjects refused to follow due to personal reasons and were lost to followup."</p> <p>Comment: large difference in missingness among the intervention groups. No description of how to handle missing data.</p>
Selective reporting (reporting bias)	High risk	No trial protocol available. Glycaemic measures not reported, hypoglycaemia and adverse events reported in a format that make them unsuitable for meta-analysis.
Other bias	Low risk	No other sources of bias identified

Ji 2011

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1
Participants	Inclusion criteria: no history of diabetes or autoimmune disease, and no acute or chronic infection within 2 weeks before enrolment, IFG and/or IGT.

Ji 2011 (Continued)

Exclusion criteria: not reported

Diagnostic criteria: WHO 1999 (IGT (2hPG between 7.8 mmol/L and 11.0 mmol/L); or IFG (FPG between 6.1 mmol/L and 6.9 mmol/L))

Interventions

Number of study centres: 1

Run-in period: not reported

Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of intervention

Extension period: none

Outcomes

Composite outcome measures reported: none

Study details

Trial terminated early: no

Publication details

Language of publication: Chinese

Funding: non-commercial funding (governmental funding)

Publication status: peer-reviewed journal, full-article

Stated aim of study

Quote from publication: "To observe the changes of serum, hs-crp and insulin sensitivity index before and after metformin treatment or intensive lifestyle intervention in patients with prediabetes."

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "randomised" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)

Ji 2011 (Continued)

Incomplete outcome data (attrition bias) incidence of T2DM	Low risk	Quote from publication: "No patients were discontinued due to adverse drug reactions." Comment: reported (no missing data)
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	Quote from publication: "No patients were discontinued due to adverse drug reactions." Comment: reported (no missing data)
Selective reporting (reporting bias)	High risk	Comment: protocol unavailable. Adverse events not reported. Likely to have been assessed and evaluated during the study
Other bias	Low risk	Comment: no other risk of bias identified

Jin 2009

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1	
Participants	Inclusion criteria: IFG Exclusion criteria: severe cardiovascular and cerebrovascular diseases and obvious abnormal liver and kidney functions Diagnostic criteria: IFG diagnosed from WHO 1999 criteria (FPG between 6.1 mmol/L to 6.9 mmol/L, 2-hour postprandial blood glucose (2hPG) < 7.8 mmol/L)	
Interventions	Number of study centres: 1 Run-in period: not reported Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of intervention Extension period: none	
Outcomes	Composite outcomes measures reported: none	
Study details	Trial terminated early (for benefit/because of adverse events): no	
Publication details	Language of publication: Chinese Funding: non-commercial (government funding) Publication status: peer-reviewed, full-article	
Stated aim of study	Quote from publication: "To observe the changes of islet cell function and insulin resistance (IR) in patients with impaired fasting glucose after different methods of intervention, and to explore the pathogenesis and intervention pathway of IFG."	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "randomised"

Jin 2009 (Continued)

		Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	<p>Quote from publication: "During the treatment, 1 patient in the rosiglitazone group had facial edema and 2 patients in the rosiglitazone group had intolerance of both lower limbs and withdrew from the study. Three patients in the metformin group were withdrawn from the study due to severe gastrointestinal reactions. No significant adverse reactions or hypoglycemia were observed in other patients."</p> <p>Comment: PP analysis was used (reported and reasons explained)</p>
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	<p>Quote from publication: "During the treatment, 1 patient in the rosiglitazone group had facial edema and 2 patients in the rosiglitazone group had intolerance of both lower limbs and withdrew from the study. Three patients in the metformin group were withdrawn from the study due to severe gastrointestinal reactions. No significant adverse reactions or hypoglycemia were observed in other patients."</p> <p>Comment: PP analysis was used (reported and reasons explained)</p>
Selective reporting (reporting bias)	Unclear risk	Comment: protocol unavailable
Other bias	Low risk	Comment: no other risk of bias identified

Li 1999

Methods	Parallel randomised controlled trial, randomisation ratio 1:1
Participants	<p>Inclusion criteria: participants aged 30 years to 60 years with IGT</p> <p>Exclusion criteria: diabetes, a history of ischaemic heart disease or renal or hepatic disorders, and previous treatment with metformin</p>

Li 1999 (Continued)

Diagnostic criteria: WHO 1985 (IGT (2hPG 140 mg/dL to 200 mg/dL [7.8 mmol/L to 11.0 mmol/L]) and FPG <140 mg/dL (7.8 mmol/L))

Interventions	<p>Number of study centres: -</p> <p>Run-in period: not described</p> <p>Administration-free period before testing during trial: not reported</p> <p>Extension period: no</p>
Outcomes	<p>Composite outcome measures reported: none</p>
Study details	<p>Trial terminated early: no</p> <p>Taking trial drug on glycaemic testing days: not specified</p>
Publication details	<p>Language of publication: English</p> <p>Funding: not described</p> <p>Publication status: peer-reviewed journal</p>
Stated aim of study	<p>Quote from publication: "To evaluate the effect of metformin on glucose metabolism, insulin sensitivity and rate of conversion diabetes in people with impaired glucose tolerance (IGT)."</p>
Notes	<p>The placebo was provided by the manufacturer of metformin, Beijing Tian-An United Pharmaceutical Co. Ltd. (Tokyo, Japan)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote from publication: "People meeting the entry criteria were randomized under double-blind conditions to receive either placebo or metformin at a dosage of 250 mg three times daily for a duration of 12 months."</p> <p>Comment: insufficient information about the sequence generation</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no description of allocation concealment</p>
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Quote from publication: "People meeting the entry criteria were randomized under double-blind conditions to receive either placebo or metformin at a dosage of 250 mg three times daily for a duration of 12 months."</p> <p>Comment: blinding of participants and key study personnel ensured</p>
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Quote from publication: "People meeting the entry criteria were randomized under double-blind conditions to receive either placebo or metformin at a dosage of 250 mg three times daily for a duration of 12 months."</p> <p>Comment: blinding of participants and key study personnel ensured</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Quote from publication: "People meeting the entry criteria were randomized under double-blind conditions to receive either placebo or metformin at a dosage of 250 mg three times daily for a duration of 12 months."</p> <p>Comment: possible blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding.</p>

Li 1999 (Continued)

Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	<p>Quote from publication: "People meeting the entry criteria were randomized under double-blind conditions to receive either placebo or metformin at a dosage of 250 mg three times daily for a duration of 12 months."</p> <p>Comment: possible blinding of outcome assessment, but the outcome is not likely to be influenced by lack of blinding.</p>
Incomplete outcome data (attrition bias) incidence of T2DM	Low risk	<p>Quote from publication: "On an intention-to-treat basis, excluding only five patients lost to follow-up, 32 of the metformin treated subjects became normally glucose tolerant (76.2%) compared to 23 (53.5%) for placebo patients. Six patients on placebo converted to frank diabetes (14.0%) and this compared to three patients (7.1%) on metformin, P = 0.091, Table 3."</p> <p>Comment: the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate</p>
Incomplete outcome data (attrition bias) measures of blood glucose control	Unclear risk	<p>Quote from publication: "Twelve subjects were excluded from the metformin group for the following reasons: tablet noncompliance, seven; loss to follow-up, three; and gastrointestinal side-effects, two. Eight subjects were excluded from the placebo group as follows: tablet noncompliance, five; loss to follow-up, two; and raised liver enzymes, one."</p> <p>Comment: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias</p>
Selective reporting (reporting bias)	High risk	<p>Comment: no trial protocol available. Likely that hypoglycaemia is measured but not reported.</p>
Other bias	Unclear risk	<p>Comment: unclear funding source</p>

Li 2009

Methods	Parallel randomised controlled trial, randomisation ratio 1:1
Participants	<p>Inclusion criteria: obesity (BMI of 25 kg/m² or more) and impaired regulation of glucose</p> <p>Exclusion criteria: not reported</p> <p>Diagnostic criteria: WHO 1999 (FPG between 6.1 mmol/L to 6.9 mmol/L, 2-hour glucose (2hPG) between 7.8 mmol/L to 11.0 mmol/L)</p>
Interventions	<p>Number of study centres: 1</p> <p>Run-in period: not reported</p> <p>Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of intervention</p> <p>Extension period: none</p>
Outcomes	Composite outcome measures reported: none
Study details	Trial terminated early (for benefit/because of adverse events): no
Publication details	<p>Language of publication: Chinese</p> <p>Funding: not reported</p>

Li 2009 (Continued)

Publication status: peer-reviewed journal, full article

Stated aim of study **Quote from publication:** "In this study, metformin was used to treat obese people with impaired regulation of mixed sugars, so as to explore the methods of diabetes intervention."

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "randomised" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	Comment: a total of 7 participants (3:4) lost to follow-up, no explanation provided, PP analysis was used (only reported)
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	Comment: a total of 7 participants (3:4) lost to follow-up, no explanation provided, ITT analysis was used (only reported)
Selective reporting (reporting bias)	Unclear risk	Comment: protocol unavailable
Other bias	Unclear risk	Comment: unknown funding source

Liao 2012

Methods **Parallel randomised controlled trial, randomisation ratio 1:1**

Liao 2012 (Continued)

Participants	<p>Inclusion criteria: IGT. All participants were not treated with any glucose-lowering drugs before inclusion, and were treated with simple diet and exercise for 3 months, with unsatisfactory results and no obvious adverse reactions. All participants had no serious diseases of gastrointestinal tract, heart, liver, kidney and other important organs</p> <p>Exclusion criteria: blood glucose abnormalities caused by other diseases</p> <p>Diagnostic criteria: WHO 1999 (FPG between 6.1 mmol/L to 6.9 mmol/L, 2hPG between 7.8 mmol/L to 11.0 mmol/L)</p>	
Interventions	<p>Number of study centres: 1</p> <p>Run-in period: 3 months</p> <p>Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of intervention</p> <p>Extension period: none</p>	
Outcomes	<p>Composite outcome measures reported: none</p>	
Study details	<p>Trial terminated early (for benefit/because of adverse events): no</p>	
Publication details	<p>Language of publication: Chinese</p> <p>Funding: not reported</p> <p>Publication status: peer-reviewed journal, full-article</p>	
Stated aim of study	<p>Quote from publication: "To compare the effectiveness and security of acarbose and metformin in the treatment for impaired glucose tolerance"</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote from publication: "randomised"</p> <p>Comment: insufficient information about the sequence generation process</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no description of allocation concealment</p>
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>

Liao 2012 (Continued)

Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	Quote from publication: "In the acarbose group, 2 cases were lost after 1 year of follow-up, 1 case of lung cancer and 1 case of hepatitis. In the metformin group, 1 case of cerebral hemorrhage was lost after 1 year of follow-up." Comment: PP analysis was used (reported and reasons explained)
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	Quote from publication: "In the acarbose group, 2 cases were lost after 1 year of follow-up, 1 case of lung cancer and 1 case of hepatitis. In the metformin group, 1 case of cerebral hemorrhage was lost after 1 year of follow-up." Comment: PP analysis was used (reported and reasons explained)
Selective reporting (reporting bias)	High risk	Comment: protocol unavailable. Outcomes that were not mentioned in the method section were reported in the result section (e.g. adverse events)
Other bias	Unclear risk	Comment: funding source not described

Lu 2002

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1:1
Participants	Inclusion criteria: IGT Exclusion criteria: not reported Diagnostic criteria: WHO 1985 (IGT 2hPG of 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.0 mmol/L))
Interventions	Number of study centres: not reported (12 authors from 5 departments in 2 hospitals) Run-in period: not reported Administration-free period before testing during trial: did not take study-drug on the morning of the OGTT retest Extension period: none
Outcomes	Composite outcome measures reported: none
Study details	Trial terminated early (for benefit/because of adverse events): no
Publication details	Language of publication: Chinese Funding: military funding Publication status: peer-reviewed journal, full-article
Stated aim of study	Quote from publication: "To evaluate the efficacy of metformin and diet fibre intervention in preventing the conversion of impaired glucose tolerance (IGT) to type 2 diabetes mellitus."
Notes	
Risk of bias	

Lu 2002 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "randomised" Comment: insufficient information about the sequence generation process
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) all-cause mortality/cardiovascular mortality	Low risk	Comment: no blinding reported, however, mortality is unlikely to be influenced by lack of blinding. (adjudicated outcome measurement)
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) all-cause mortality/cardiovascular mortality	Low risk	Comment: no blinding reported, however, mortality is unlikely to be influenced by lack of blinding. (adjudicated outcome measurement)
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	Quote from publication: "A total of 23 patients withdrew, and the withdrawal rate was 7.8%. Among the 72 cases in the education group, 7 cases quit without definite reason, and 1 case died of cerebral thrombosis complicated with pulmonary infection. Six cases in the education + diet instruction group were lost to follow-up. In the dietary fiber group, 3 patients lost follow-up and 1 patient withdrew from gastric cancer. In the metformin group, 3 patients were lost to follow-up, and 2 patients withdrew due to going abroad." Comment: reason acceptable, but PP analysis was used (reported and reasons explained)
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	Quote from publication: "A total of 23 patients withdrew, and the withdrawal rate was 7.8%. Among the 72 cases in the education group, 7 cases quit without definite reason, and 1 case died of cerebral thrombosis complicated with pulmonary infection. Six cases in the education + diet instruction group were lost to follow-up. In the dietary fiber group, 3 patients lost follow-up and 1 patient withdrew from gastric cancer. In the metformin group, 3 patients were lost to follow-up, and 2 patients withdrew due to going abroad."

Lu 2002 (Continued)

		Comment: reason acceptable, but PP analysis was used (reported and reasons explained)
Selective reporting (reporting bias)	High risk	Comment: protocol unavailable. Outcomes not described in the method section were reported in the results (adverse events)
Other bias	Low risk	Comment: no other risk of bias identified

Lu 2010

Methods	Parallel randomised controlled trial, randomisation ratio 1:1	
Participants	<p>Inclusion criteria: (1) participants with pre-diabetes; (2) 25 to 80 years old; (3) twice increased fasting blood glucose (fasting blood glucose 5.6 mmol/L to 6.9 mmol/L); (4) postprandial blood glucose was increased (OGTT 2-hour blood glucose 7.8 mmol/L to 11.1 mmol/L).</p> <p>Exclusion criteria: (1) participants with cardiovascular diseases, hepatitis, kidney diseases and other basic diseases that may increase the risk of intervention; (2) participants who may affect the process of the experiment: inability to follow up, refusal of random grouping, pregnancy and lactation, etc., (3) participants were taking drugs that could interfere with the test results, such as diuretics, beta-blockers 13 and glucocorticoids.</p> <p>Diagnostic criteria: ADA 2009 (fasting blood glucose 5.6 mmol/L to 6.9 mmol/L or 2-hour blood glucose 7.8 mmol/L to 11.1 mmol/L).</p>	
Interventions	<p>Number of study centres: 1</p> <p>Run-in period: not reported</p> <p>Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of intervention</p> <p>Extension period: none</p>	
Outcomes	Composite outcome measures reported: none	
Study details	<p>Trial identifier: unregistered</p> <p>Trial terminated early (for benefit/because of adverse events): no</p>	
Publication details	<p>Language of publication: Chinese</p> <p>Funding: not reported</p> <p>Publication status: peer-reviewed journal, full article</p>	
Stated aim of study	<p>Quote from publication: "This study is a clinical demonstration study on lifestyle adjustment and metformin intervention, two commonly used measures to prevent or delay diabetes. Through the comparison and analysis of the blood glucose index changes after the implementation, the compliance of the two kinds of intervention measures, weight changes, the incidence of adverse events and other indicators, the efficacy and safety were reasonably evaluated, and the most reasonable, effective and practical measures for preventing or delaying diabetes were finally determined."</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement

Lu 2010 (Continued)

Random sequence generation (selection bias)	Unclear risk	<p>Quote from publication: "randomised"</p> <p>Comment: insufficient information about the sequence generation process</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no description of allocation concealment</p>
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>
Incomplete outcome data (attrition bias) incidence of T2DM	Low risk	<p>Quote from publication: "A total of 100 patients in the lifestyle intervention group completed the study, 17 patients withdrew from the study (2 patients went abroad, 15 patients for personal reasons), and the baseline characteristics of those who did not complete the study were the same as those who completed the study. 111 patients (6 without follow-up) entered the primary and secondary endpoint analysis. In the metformin group, 21 patients withdrew from the study (6 with gastrointestinal reactions, 10 with personal reasons, 5 with other reasons), and 115 patients entered the primary and secondary endpoint analysis (2 without follow-up)."; "last observation carried forward (LOCF) was used"; "Since our study included observational studies of compliance, our analysis showed that the LOCF did not affect the interpretation of the results of this study."</p> <p>Comment: reported, acceptable reason, and appropriate imputation of data (reported and reasons explained)</p>
Incomplete outcome data (attrition bias) measures of blood glucose control	Low risk	<p>Quote from publication: "A total of 100 patients in the lifestyle intervention group completed the study, 17 patients withdrew from the study (2 patients went abroad, 15 patients for personal reasons), and the baseline characteristics of those who did not complete the study were the same as those who completed the study. 111 patients (6 without follow-up) entered the primary and secondary endpoint analysis. In the metformin group, 21 patients withdrew from the study (6 with gastrointestinal reactions, 10 with personal reasons, 5 with other reasons), and 115 patients entered the primary and secondary endpoint analysis (2 without follow-up)."; "last observation carried forward (LOCF) was used"; "Since our study included observational studies of compliance, our analysis showed that the LOCF did not affect the interpretation of the results of this study."</p> <p>Comment: reported, acceptable reason, and appropriate imputation of data (reported and reasons explained)</p>

Lu 2010 (Continued)

Selective reporting (reporting bias)	Unclear risk	Comment: protocol unavailable
Other bias	Unclear risk	Comment: unknown funding source

Maji 2005

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1:1	
Participants	Inclusion criteria: IGT Exclusion criteria: NR Diagnostic criteria: IGT (2hPG 110 to 200 mg/dL [6.1 mmol/L to 11.0 mmol/L]) and FPG <1 10mg/dL (6.1 mmol/L)	
Interventions	Number of study centres: NR Run-in period: participants with IGT were selected and given diet and lifestyle advice for three months. The participants who still had IGT were thereafter randomised Administration-free period before testing during trial: not reported Extension period: no	
Outcomes	Composite outcome measures reported: no	
Study details	Trial terminated before regular end (for benefit/because of adverse events): no Taking trial drug on glycaemic testing days: NR	
Publication details	Language of publication: English Funding: NR Publication status: peer-reviewed journal	
Stated aim of study	Quote from publication: "The present study of diabetes prevention programme has been started in 2001 at Ramakrishna Mission Seva Pratishthan to assess the nature and extent if interventional therapies regarding prevention of type 2 diabetes"	
Notes	2-hour OGTT; HbA1c; FPG were reported as per cent change from baseline; not possible to include data in the meta-analysis. There were no significant change in the percent reduction of glycaemic parameters in between the three groups receiving a pharmacological intervention	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "Those who still had their blood sugar at the IGT range were randomised into 3 groups to receive either metformin or rosiglitazone or acarbose." Comment: insufficient information about the sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment

Maji 2005 (Continued)

Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Quote from publication: "...no person in the study group developed diabetes during this period of three years, .."</p> <p>Comment: no blinding, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Comment: no blinding, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Quote from publication: "...no person in the study group developed diabetes during this period of three years, .."</p> <p>Comment: no blinding, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	<p>Comment: no blinding, the outcome is not likely to be influenced by lack of blinding</p>
Incomplete outcome data (attrition bias) incidence of T2DM	Unclear risk	<p>Comment: not mentioned in the publication how missing data were handled</p>
Incomplete outcome data (attrition bias) measures of blood glucose control	Unclear risk	<p>Comment: not mentioned in the publication how missing data were handled or how many included in the analyses</p>
Selective reporting (reporting bias)	High risk	<p>No trial protocol available. Glycaemic parameters reported in a format that made them unsuitable for meta-analysis. Data on hypoglycaemia and adverse events were not reported</p>
Other bias	Unclear risk	<p>No funding source reported</p>

Papoz 1978

Methods	Parallel randomised controlled clinical trial, randomisation ratio 1:1	
Participants	<p>Inclusion criteria: male, 25 to 55 years, 'borderline' diabetes (see criteria in the section 'diagnostic criteria')</p> <p>Exclusion criteria: NR</p> <p>Diagnostic criteria: fasting blood glucose ≥ 5.6 mmol/L and < 7.2 mmol/L or 2-hour blood glucose after a 75 g oral glucose challenge ≥ 6.7 mmol/L and < 8.3 mmol/L; when these criteria for intermediate hyperglycaemia were fulfilled, a second test was performed: blood glucose concentrations were determined fasting at 15, 30, 60, 120, 180, 240 and 300 minutes after an oral glucose load. Eligible individuals had 2-hour blood glucose concentrations ≥ 6.7 mmol/L but < 8.3 mmol/L or fasting blood glucose concentrations ≥ 5.6 mmol/L and < 7.2 mmol/L; blood glucose after 30 minutes ≥ 8.9 mmol/L and < 12.2 mmol/L; blood glucose after 60 minutes ≥ 8.9 mmol/L and < 12.2 mmol/L (the European Diabetes Epidemiology Study Group 1970 criteria)</p>	
Interventions	Number of study centres: 1	

Papoz 1978 (Continued)

Run-in period: none

Administration-free period before testing during trial: participants received study-drug on the day of testing blood glucose at 2 months and 14 months. However, the last glycaemic measurements were performed 15 days after the study drug was stopped

Extension period: none

Outcomes	Composite outcome measures reported: no
Study details	Trial terminated early: no
Publication details	Language of publication: English Funding: non-commercial funding Publication status: peer-reviewed journal
Stated aim of study	Quote from publication: "A double blind controlled clinical trial was undertaken to test the effectiveness of oral hypoglycaemic drugs in improving blood glucose and plasma insulin levels of borderline diabetic patients"
Notes	Blood glucose values in this trial were reported as whole blood glucose. In the tables and result section all values are converted to plasma glucose values (diabetes.co.uk)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote from publication: "They were randomized into 4 groups according..." Comment: method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Quote from publication: "A double blind controlled clinical trial was undertaken..." Comment: investigator-assessed, double-blinding
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Quote from publication: "A double blind controlled clinical trial was undertaken..." Comment: investigator-assessed, double-blinding
Incomplete outcome data (attrition bias) measures of blood glucose control	Unclear risk	Quote from publication: "Thirty four patients (24 during the first year, 10 during the second year of the study) were lost to follow-up; they came equally from the four different treatment groups and exhibited similar baseline characteristics to the follow-up patients. Their removal from the trial did not introduce any bias into the study" Comment: the number of participants lost to follow-up are reported, but no reasons explained
Selective reporting (reporting bias)	High risk	Comment: likely that adverse events have been evaluated, but not reported (see Appendix 8)
Other bias	Low risk	Comment: the trial appeared to be free of other sources of bias

PREVENT-DM 2017

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1	
Participants	<p>Inclusion criteria: Latinas aged 20 years or more, IFG (FPG of 100 to 125 mg/dL) and/or elevated HbA1c of 5.7% to 6.4% (39 mmol/mol to 46 mmol/mol), BMI at 23 kg/m² or more</p> <p>Exclusion criteria: diabetes at baseline, were currently pregnant or planned to become pregnant, or were participating in a supervised weight loss program. Blood pressure at or above 160 mmHg/100 mmHg, contraindication to metformin, chronic conditions that could affect a participant's ability to participate (e.g. severe osteoarthritis), medical co morbidities that could influence body weight (e.g. uncontrolled thyroid disease), or medications that could affect weight or glucose metabolism (e.g., oral corticosteroids).</p> <p>Diagnostic criteria: IFG (FPG of 100 mg/dL to 125 mg/dL (5.6 mmol/L to 6.9 mmol/L) and/or intermediate elevated HbA1c of 5.7% to 6.4% (39 mmol/mol to 46 mmol/mol))</p>	
Interventions	<p>Number of study centres: one</p> <p>Run-in period: none</p> <p>Administration-free period before testing during trial: not reported</p> <p>Extension period: no</p>	
Outcomes	Composite outcome measures reported: no	
Study details	Trial terminated before regular end (for benefit/because of adverse events): no	
Publication details	<p>Language of publication: English</p> <p>Funding: non-commercial funding</p> <p>Publication status: peer-reviewed journal</p>	
Stated aim of study	Quote from publication: "This study was designed to compare the real-world effectiveness of ILI, metformin, and standard care among Hispanic women (Latinas) with prediabetes"	
Notes	Quote from publication: "Though all participants had prediabetes by HbA1c or fasting plasma glucose criteria, more participants qualified for the study based on elevated HbA1c alone (n=53, 57.6% of total participants). Among the remaining 39 participants, 12 (13.0%) qualified by having impaired fasting glucose alone, and 27 (29.3%) met both glycemic criteria for prediabetes"	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote from publication: "The random allocation sequence was generated independently by a statistician and concealed in individually sealed envelopes accessible only to the research coordinator, who ultimately assigned participants to the study interventions."</p> <p>Comment: adequate description of the sequence generation</p>
Allocation concealment (selection bias)	Low risk	<p>Quote from publication: "The assignment for each randomized group was concealed in individually-sealed, opaque envelopes kept in a locked filing cabinet accessible only to the research coordinator, who ultimately assigned participants to the study interventions."</p> <p>Comment: adequate description of the allocation concealment</p>

PREVENT-DM 2017 (Continued)

Blinding of participants and personnel (performance bias) all-cause mortality/cardiovascular mortality	Low risk	<p>Quote from publication: "The nature of the study interventions precludes blinding participants, promotoras, or the research coordinator to treatment assignments."</p> <p>Comment: no blinding, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Quote from publication: "The nature of the study interventions precludes blinding participants, promotoras, or the research coordinator to treatment assignments."</p> <p>Comment: no blinding, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) all-cause mortality/cardiovascular mortality	Low risk	<p>Quote from publication: "The nature of the study interventions precludes blinding participants, promotoras, or the research coordinator to treatment assignments."</p> <p>Comment: no blinding, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Quote from publication: "The nature of the study interventions precludes blinding participants, promotoras, or the research coordinator to treatment assignments."</p> <p>Comment: no blinding, the outcome is not likely to be influenced by lack of blinding</p>
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	
Incomplete outcome data (attrition bias) all-cause mortality/cardiovascular mortality	Low risk	<p>Quote from publication: "Data will be analyzed assuming an intent-to-treat approach where all randomized subjects are analyzed according to their treatment assignment, regardless of adherence."</p> <p>Comment: the number of participants who were lost to follow-up or excluded due to pregnancy were low (2 in metformin and standard care; three in intensive diet plus exercise group)</p>
Incomplete outcome data (attrition bias) incidence of T2DM	Low risk	<p>Quote from publication: "Data will be analyzed assuming an intent-to-treat approach where all randomized subjects are analyzed according to their treatment assignment, regardless of adherence."</p> <p>Comment: the numbers of participants who were lost to follow-up or excluded due to pregnancy were low (2 in metformin and standard care; three in intensive diet plus exercise group)</p>
Selective reporting (reporting bias)	High risk	Likely hypoglycaemia was evaluated, but no data provided
Other bias	Low risk	No other sources of bias identified

Wang 2009

Methods	Parallel randomised controlled trial, randomisation ratio 1:1
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Wang 2009 (Continued)

Participants	<p>Inclusion criteria: IGT and/or IFG</p> <p>Exclusion criteria: hyperthyroidism, hypercortisolism and acromegaly; blood glucose abnormalities caused by pancreatic exocrine gland dysfunction and liver function damage</p> <p>Diagnostic criteria: ADA 1997 (FPG 5.6 mmol/L to 6.9 mmol/L, and/or 2hPG 7.8 mmol/L to 11.0 mmol/L)</p>	
Interventions	<p>Number of study centres: 1</p> <p>Run-in period: not reported</p> <p>Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of intervention</p> <p>Extension period: none</p>	
Outcomes	<p>Composite outcome measures reported: none</p>	
Study details	<p>Trial terminated early (for benefit/because of adverse events): no</p>	
Publication details	<p>Language of publication: Chinese</p> <p>Funding: not reported</p> <p>Publication status: conference proceedings</p>	
Stated aim of study	<p>Quote from publication: "To observe the effect of metformin on 30 patients with impaired glucose regulation (IGR), and to explore the intervention method in the prediabetes stage."</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote from publication: "randomised"</p> <p>Comment: insufficient information about the sequence generation process</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no description of allocation concealment</p>
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)</p>
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)</p>

Wang 2009 (Continued)

Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Incomplete outcome data (attrition bias) incidence of T2DM	High risk	<p>Quote from publication: "In the treatment group, 2 patients showed gastrointestinal reactions after taking the medicine, and the discomfort symptoms disappeared after stopping the medicine, which was considered as adverse drug reactions, so they were withdrawn from the study."</p> <p>Comment: PP analysis was used (2/30 = 6.7%); however, if the two who were absent from analysis had developed T2DM the incidence would have been doubled (4/32 = 12.5%)</p>
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	<p>Quote from publication: "In the treatment group, 2 patients showed gastrointestinal reactions after taking the medicine, and the discomfort symptoms disappeared after stopping the medicine, which was considered as adverse drug reactions, so they were withdrawn from the study."</p> <p>Comment: the author did not report the number of participants included in the FBG and 2hPG analyses, possibly PP analyses were applied</p>
Selective reporting (reporting bias)	Unclear risk	Comment: protocol unavailable
Other bias	Unclear risk	Comment: unknown funding source

Zeng 2013

Methods	Parallel randomised controlled trial, randomisation ratio 1:1:1
Participants	<p>Inclusion criteria: impaired fasting glucose with or without IGT</p> <p>Exclusion criteria: liver and kidney dysfunction; severe cardiovascular and cerebrovascular diseases</p> <p>Diagnostic criteria: WHO 1999 (IFG FPG 6.1 to 6.9 mmol/L; IGT 2hPG ≥7.8 mmol/L to <11.1 mmol/L)</p>
Interventions	<p>Number of study centres: 1</p> <p>Run-in period: NR</p> <p>Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of intervention</p> <p>Extension period: none</p>
Outcomes	Composite outcome measures reported: none
Study details	Trial terminated early (for benefit/because of adverse events): no
Publication details	<p>Language of publication: Chinese</p> <p>Funding: not reported</p> <p>Publication status: peer-reviewed journal, full-article</p>
Stated aim of study	Quote from publication: "To evaluate the clinical effects of different interventions on impaired glucose regulation."

Zeng 2013 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from publication: "random number table" Comment: adequate description of the sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: no description of allocation concealment
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)
Incomplete outcome data (attrition bias) incidence of T2DM	Unclear risk	Comment: no exclusion reported, however, unclear whether re-inclusion applied (not reported)
Incomplete outcome data (attrition bias) measures of blood glucose control	Unclear risk	Comment: no exclusion reported, however, unclear whether re-inclusion applied (not reported)
Selective reporting (reporting bias)	High risk	Comment: protocol unavailable. Adverse events not reported- likely this outcome has been evaluated
Other bias	Unclear risk	Comment: unknown funding source

Zhao 2013

Methods	Parallel randomised controlled trial, randomisation ratio 1:1
Participants	Inclusion criteria: IGT, IFG, BMI > 25 kg /m ² , waist to hip ratio ≥ 0.9 for males and ≥ 0.85 for females Exclusion criteria: impaired liver and kidney function, severe heart and lung disease, infection, surgery and heavy alcohol consumption

Zhao 2013 (Continued)

Diagnostic criteria: WHO 1999 (FPG between 5.6 mmol /L ~ 6.9 mmol /L, 2hPG 7.8 mmol /L ~ 11.0 mmol/L)

Interventions	<p>Number of study centres: 1</p> <p>Run-in period: not reported</p> <p>Administration-free period before testing during trial: not specified if any study drug was taken on the testing day at the end of intervention</p> <p>Extension period: none</p>	
Outcomes	<p>Composite outcome measures reported: none</p>	
Study details	<p>Trial terminated early (for benefit/because of adverse events): no</p>	
Publication details	<p>Language of publication: Chinese</p> <p>Funding: not reported</p> <p>Publication status: peer-reviewed journal, full-article</p>	
Stated aim of study	<p>Quote from publication: "We used metformin combined with lifestyle intervention to treat obese patients with pre-diabetes."</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote from publication: "randomised"</p> <p>Comment: insufficient information about the sequence generation process</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: no description of allocation concealment</p>
Blinding of participants and personnel (performance bias) incidence of T2DM	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>
Blinding of participants and personnel (performance bias) measures of blood glucose control	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding. (investigator-assessed outcome measurement)</p>
Blinding of outcome assessment (detection bias) incidence of T2DM	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)</p>
Blinding of outcome assessment (detection bias) measures of blood glucose control	Low risk	<p>Comment: no blinding reported, however, laboratory indexes are unlikely to be influenced by lack of blinding (investigator-assessed outcome measurement)</p>

Zhao 2013 (Continued)

Incomplete outcome data (attrition bias) incidence of T2DM	High risk	Quote from publication: "In the treatment group, 1 patient withdrew due to gastrointestinal reaction (diarrhea); no case was lost to follow-up in both groups." Comment: PP analysis was used (reported and reasons explained)
Incomplete outcome data (attrition bias) measures of blood glucose control	High risk	Quote from publication: "In the treatment group, 1 patient withdrew due to gastrointestinal reaction (diarrhea); no case was lost to follow-up in both groups." Comment: PP analysis was applied (reported and reasons explained)
Selective reporting (reporting bias)	High risk	Comment: protocol unavailable. Have only reported non-serious adverse effects. It is likely that serious adverse effect have been collected as well, but not reported
Other bias	Unclear risk	Comment: funding source not reported

2hPG: 2-hour plasma glucose value after glucose tolerance test; **ADA:** American Diabetes Association; **BMI:** body mass index; **DBP:** diastolic blood pressure; **FPG:** fasting plasma glucose; **HbA1c:** glycosylated haemoglobin A1c; **IGT:** impaired glucose tolerance; **IFG:** impaired fasting glucose; **ITT:** intention to treat; **NIDDM:** non-insulin-dependent diabetes mellitus; **NR:** not reported; **NYHA:** New York Heart Association; **OGTT:** oral glucose tolerance test; **PP:** per protocol; **RCT:** randomised controlled trial; **SAE:** serious adverse events; **SBP:** systolic blood pressure; **T2DM:** type 2 diabetes mellitus; **WHO:** World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Acbay 1996	Duration of the intervention less than one year
Ballon 2011	Duration of the intervention less than one year
Biarnés 2005	Duration of the intervention less than one year
Bulcão 2007	Duration of the intervention less than one year
Caballero 2004	Duration of the intervention less than one year
Celik 2012	Wrong population
Chazova 2006	Duration of the intervention less than one year
Chen 2013	Translated from Chinese: wrong intervention. Co-intervention not identical.
ChiCTR-TRC-09000548	Duration of intervention less than one year (information provided by author)
CTRI/2013/02/003417	Study protocol for non-randomised study
Eguchi 2007	Duration of the intervention less than one year
Esteghamati 2013	Duration of the intervention less than one year
EUCTR-000650-21-ES	Not a RCT
EUCTR2008-004497-40-GB	Not a RCT

Study	Reason for exclusion
Fleming 2002	Wrong population
Flores-Saenz 2003	Duration of the intervention less than one year
Gore 2005	Duration of the intervention less than one year
Gram 2011	Wrong population
Guardado-Mendoza R 2018	Wrong intervention/comparator
Gómez-Díaz 2012	Duration of the intervention less than one year
Haukeland 2008	Wrong population
Ishida 2005	Not a RCT (translated from Japanese: narrative review explaining the history, mechanism and side effects of metformin)
Kato 2009	Wrong population
Kelly 2012	Duration of the intervention less than one year
Kendall 2013	Duration of the intervention less than one year
Kilic 2011	Duration of the intervention less than one year
Koev 2004	Duration of the intervention less than one year
Krysiak 2012	Duration of the intervention less than one year
Lehtovirta 2001	Duration of the intervention less than one year
Li 2009b	Duration of the intervention less than one year
LIMIT-1	Duration of the intervention less than one year
Lu 2011	Wrong intervention/comparator (not identical concomitant intervention)
Malin 2013	Duration of the intervention less than one year
Medical letter	Not a RCT
Morel 1999	Duration of the intervention less than one year
NCT00108615	Duration of the intervention less than one year
NCT02338193	Duration of the intervention less than one year
NCT03258723	Wrong population
Pre-DICTED	Wrong intervention/comparator
RESIST	Duration of the intervention less than one year
Retnakaran 2012	Duration of the intervention less than one year

Study	Reason for exclusion
Rodríguez-Moctezuma 2005	Wrong population
Scheen 2009	Wrong population
Schuster 2004	Non-prediabetic population
SLCTR/2016/026	Duration of the intervention less than one year
STOP-NIDDM	Wrong intervention (does not randomise to metformin)
Stroup 2013	Duration of the intervention less than one year
Sultana 2012	Duration of the intervention less than one year
UKPDS	Wrong population
Vitolins 2017	Not a RCT
Wan 2010	Duration of intervention less than one year
Zinman 2010	Wrong intervention/comparator

RCT: randomised clinical trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

ChiCTR-IPR-17012309

Methods	Randomised, parallel, interventional study
Participants	Inclusion criteria: according to the classification standard of WHO glucose metabolism status (1999), IGR was diagnosed two weeks before randomisation; aged 35 to 60 years; no use of glucose-lowering drugs (including herbal medicine for lowering blood glucose); women who are male or non-pregnant, non-lactating, and have no family planning for the next three years; BMI 24 kg/m ² to < 32 kg/m ²
Interventions	Metformin plus lifestyle intervention versus lifestyle intervention
Outcomes	Height, weight, blood pressure, fat, blood glucose, insulin, endothelial progenitor cells
Publication details	Trial register record: ChiCTR-IPR-17012309
Notes	Not clarified if study can be included, duration of intervention? Author (Ping Yu) contacted for further information (06 April.2019). No reply.

EDIT 1997

Methods	Randomised, parallel, interventional study
Participants	Participants 'at risk' for developing diabetes, fasting BG 5.5 to 7.7 mmol/L

EDIT 1997 (Continued)

Interventions	Metformin 500 mg three times daily plus placebo three times daily versus acarbose 50 mg three times daily plus placebo three times daily versus placebo three times daily plus placebo three times daily One of the intervention groups will not to be included in review (metformin 500 mg three times daily + acarbose 50 mg three times daily)
Outcomes	Incidence of T2DM, glycaemic variables
Publication details	Trial register record: ISRCTN96631607 The study is only published as abstracts
Notes	Conclusion of the trial in published abstract": "No differences were seen in relative risk for diabetes by 6 years with acarbose (1.04, P = 0.81), Metformin (0.99, P = 0.94) or combination therapy (1.02, P = 0.91). In those with IGT at baseline, relative risk was reduced significantly with acarbose (0.66, P = 0.046) but not Metformin (1.09, P = 0.70) or combination therapy (0.72, P = 0.27)." The reviewers of Van de Laar 2006 have already asked for supplemental information.

NCT02409238

Methods	Randomised, parallel, interventional study
Participants	Prediabetes (if not diabetic): IFG: ADA criteria: fasting plasma glucose level from 5.6 mmol/L (100 mg/dL) to 6.9 mmol/L (125 mg/dL), and/or IGT (WHO and ADA criteria: two-hour glucose levels of 140 mg/dL to 199 mg/dL (7.8 mmol to 11.0 mmol) on the 75 g oral glucose tolerance test and/or HbA1C: 5.7% to 6.4% (ADA criteria) People with type 2 diabetes
Interventions	Metformin plus lifestyle interventions versus standard care
Outcomes	Primary efficacy endpoint: change in cerebral glucose metabolic rate Primary cognitive endpoint: change in composite z-score of memory and multi-domain non-amnesic cognitive test performance using a neuropsychological assessment Secondary outcome measures: change in subjective memory and cognitive complaint, change in basic activities of daily living (ADL), change in cognitive instrumental ADL scale, change in global clinical dementia rating sum of boxes, change in mini-mental state examination, change in the Montreal cognitive assessment scale, change in fasting plasma insulin, change in homeostatic model assessment, change in weight, change in BMI, change in waist circumference, change in FPG, change in HbA1c, change in fasting lipids
Publication details	Trial register record: NCT02409238
Notes	The study includes prediabetic and diabetic people and data need to be separated for use in this review. Not clarified if study can be included. Authors (Wee Kien Han Andrew and Tan Kee Tung) contacted for information about if study are finished and published (30.03.2019). Answer: study neither finished nor published (04.04.2019).

Polanco 2015

Methods	Randomised, open-label clinical trial
Participants	People with prediabetes

Polanco 2015 (Continued)

Interventions	Metformin 850 mg twice daily plus lifestyle changes versus change in lifestyle
Outcomes	Quote: "The study was divided into two phases, with 2 intervention groups. In the first phase group 1 (52 patients) was treated with metformin 850 mg, 2 times a day, as well as changes in lifestyle and group 2 (50 subjects) only changes in lifestyle, were evaluated clinically and biochemically for a period of six years. In the second phase intervention was similar for all participants receiving combined treatment for 4 years, with an average follow-up of 120 months (+/- 3.5). First phase: Group one, 75% of the subjects remained with PD; 21% developed T2DM and 3.8% showed normoglycemia with a 3.5% annual T2DM conversion. In group two, 62% remained with PD and 38% developed T2DM, with an annual incidence of 6.2%. Second phase: Group one, 57% had PD, 8 subjects developed T2DM (15.8%), with an overall incidence of 22 cases (42.3%), 4.2% cases per year. While in group two, 40% continued with PD and 22% were categorized as having T2DM, with an overall prevalence of 30 cases (60% of the population), with an annual rate of development of T2DM 6%. In the analysis of all subjects an incidence of 52 cases of T2DM (50.9%) was obtained, while the rest population remained with PD. The variables that were associated with the development of T2DM were fasting glucose levels and post challenge, HbA1c, insulin levels, HOMA IR, HOMA B, HOMA S and waist circumference (p <0.001). Early intervention with changes in lifestyle concomitant use of metformin prevents more effectively the development of T2DM in high risk subjects of Western Mexico"
Publication details	Only abstract available
Notes	Not possible to clarify if study meets inclusion criteria (definition of prediabetes? study published?). No contact information

ADA: American Diabetes Association; **ADL:** activities of daily living; **BG:** blood glucose; **BMI:** body mass index; **HbA1c:** glycosylated haemoglobin A1c; **IFG:** impaired fasting glucose; **IGR:** impaired glucose regulation; **IGT:** impaired glucose tolerance; **T2D:** type 2 diabetes mellitus; **WHO:** World Health Organization.

Characteristics of ongoing studies [ordered by study ID]

CTRI/2017/09/009635

Trial name or title	A study of life style modification with and without metformin in prediabetic participants
Methods	<p>Type of trial: interventional</p> <p>Allocation: randomised</p> <p>Intervention model: parallel</p> <p>Masking: not reported</p> <p>Primary purpose: not reported</p>
Participants	<p>Condition: IFG, IGT or HbA1c 5.7% to 6.4%</p> <p>Enrollment: 90</p> <p>Inclusion criteria: BMI 18.5 to 29.9 kg/m². Non diabetic individuals with either IFG (FPG > 100 mg/dL < 126 mg/dL (> 5.6 mmol/L < 7.0 mmol/L), IGT (2hPG > 140 < 200 mg/dL) (> 7.8 mmol/L < 11.1 mmol/L), HbA1c 5.7% to 6.4%</p> <p>Exclusion criteria: type 1 or type 2 diabetes (FPG > 126 mg/dL (7.0 mmol/L), 2hPG > 200 mg/dL (11.1 mmol/L) and HbA1c > 6.5%); contraindications to metformin (chronic kidney failure, hepatic dysfunction, renal impairment) and hypersensitivity; pregnant and lactating women</p>
Interventions	<p>Intervention: metformin 250 mg twice daily plus life style modification</p> <p>Comparator: life style modification</p>

CTRI/2017/09/009635 (Continued)

	Duration of intervention: two years and six months
Outcomes	<p>Primary outcomes: conversion to normoglycaemia, IGT or IFG or intermediate elevated HbA1c, and T2DM</p> <p>Secondary outcomes: antioxidants</p> <p>Other outcomes: not reported</p>
Starting date	<p>Study start date: 08/09/2016</p> <p>Study completion date: not reported</p>
Contact information	Contact: Dr Asha B, email: dr.ashareddy@gmail.com
Trial identifier	CTRI/2017/09/009635
Notes	

ePRECIDE 2017

Trial name or title	Acronym: ePRECIDE
Methods	<p>Type of trial: efficacy trial</p> <p>Allocation: randomised</p> <p>Intervention model: parallel assignment</p> <p>Masking: double-blind</p> <p>Primary purpose: not specified in protocol</p>
Participants	<p>Condition: IGT or IFG, or both</p> <p>Enrolment: 3000</p> <p>Inclusion criteria: age 45 to 74 years; IFG (FPG 6.1-6.9 mmol/L and 2hPG < 7.8 mmol/L) or IGT (FPG < 7.0 mmol/L and 2hPG ≥ 7.8 to < 11.1 mmol/L) or both conditions; informed consent given</p> <p>Exclusion criteria: T1DM; known or unknown T2DM (including screen-detected T2DM) with or without pharmacological treatment; use of a GLP-1 receptor agonist (exenatide or other) or pramlintide or any DPP-4 inhibitor or metformin within the 3 months prior to enrolment; use of insulin or long-acting insulin analogue within 3 months prior to enrolment; any previous cardiovascular or cerebrovascular clinically documented event or revascularisation procedure; clinical evidence of macrovascular complications (overt clinical cardiovascular disease) at enrolment, including angina (stable or unstable) and evidence of previous myocardial infarction in baseline electrocardiogram; current renal replacement therapy; previous diagnosis of liver cirrhosis or chronic hepatitis, or an elevation of liver enzymes (AST and or ALT) > 3 times normal ranges; previous diagnosis of chronic heart failure (NYHA class III or higher); prior solid organ transplant or awaiting solid organ transplant; malignant neoplasm requiring chemotherapy, surgery, radiation or palliative therapy in the previous 5 years. Participants with intraepithelial squamous cell carcinoma of the skin (Bowen's disease) treated with topical 5-fluorouracil and people with basal cell skin cancer allowed to enter trial; any acute condition or exacerbation of chronic condition that would, in investigator's opinion, interfere with the initial trial visit schedule and procedures; known or suspected hypersensitivity to trial products or related products; known use of non-prescribed narcotics or illicit drugs; simultaneous participation in any other clinical trial of an investigational agent; women of childbearing potential who are pregnant (all fertile women will be tested for before randomisation), breast-feeding or intend to become pregnant; presence of cataract that impedes the retinal evaluation of</p>

ePRECIDE 2017 (Continued)

both eyes; other previously diagnosed retinal diseases; any diseases that would prevent the measurement of primary endpoints; dementia, mental disorder or evident cognitive impairment unable to give informed consent; end-stage or metastatic cancer; institutionalisation; renal function impairment: GFR < 60 mL/minute/1.73 m².; contraindication to any of the study drugs (metformin or linagliptin). This includes: ALT > 3 times the upper limit of normal, history of cirrhosis or hepatitis, suspected renal artery stenosis, recent gastrointestinal bleeding (within last year), pregnant, breastfeeding or a female of childbearing potential not on reliable contraception and also any circumstance where ongoing medication might lead to potential adverse drug interaction with components of the trial medications; any other reason, medical condition, ongoing medication or significant disability that would prevent the participant complying with trial consent, treatment and follow-up procedures or potentially jeopardise her/his medical care

Interventions	<p>Intervention: 2 tablets of linagliptin 5 mg + diet and physical activity</p> <p>Comparator (1): 2 tablets of metformin 850 mg/day + diet and physical activity</p> <p>Comparator (2): 2 tablets of linagliptin 2.5 mg + metformin 850 mg plus diet and physical activity</p> <p>Comparator (3): 2 tablets of placebo + diet and physical activity</p> <p>Duration of intervention: at least 3 years, and additional follow-up to 5 years</p>
Outcomes	<p>Primary outcome: a combined continuous variable, "the microvascular complication index" (M-CI), composed of linear combination of ETDRS score, the level of urinary albumin to creatinine ratio, and sudomotor test (SUDOSCAN) score, measured during the 36th and 60th month visits.</p> <p>From email correspondence: primary purpose: prevention of complications of hyperglycaemia/prevention of progression to diabetes</p> <p>Secondary outcomes: retinopathy score at last visit defined as 2-steps' progression on ETDRS scale between baseline and visits at months 36 and 60; 1 SD increase in level of urinary albumin to creatinine ratio between baseline and visits at months 36 and 60; 1 SD decrease change in level of hands and feet conductance in SUDOSCAN between baseline and visits at months 36 and 60; change in microvascular endothelial function measured by EndoPAT method (in a subset); change in the Non-Alcoholic Fatty Liver Index (in a subset); change in biomarkers of microvascular damage, endothelial function, per-oxidation, inflammation and metabolomics (in a subset); change in the insulin secretion and β-cell function; change in self-perceived quality of life; change in symptoms of peripheral neuropathy; change in neuropsychological parameters: cognitive function, anxiety and depressive symptoms and indices; changes in obstructive sleep apnoea indices as measured by Somnomedics (in a subset); changes in ambulatory blood pressure monitoring (in a subset); change in the mean common carotid intima-media thickness (in a subset); incidence of major cardiovascular events, defined as an expanded composite of total coronary events, total stroke events, revascularisation procedures (coronary artery bypass graft, percutaneous coronary angioplasty and peripheral revascularisation), hospitalisation for heart failure, TIA and cardiovascular or cerebrovascular death. Secondary outcomes will be evaluated at 36 and 60 months</p> <p>Other outcome: none</p>
Starting date	<p>Trial start date: 2015</p> <p>Trial completion date: December 2019</p>
Contact information	<p>Responsible party/principal investigator: Prof Jaakko Tuomilehto; Prof Rafael Gabriel (co-principal investigators)</p>
Trial identifier	<p>NCT03222765; EUCTR2013-000418-39-AT</p>
Notes	<p>Multinational trial with 15 clinical centres from 12 countries: Australia, Austria, Bulgaria, Germany, Greece, Italy, Lithuania, Poland, Serbia, Spain, Switzerland and Turkey.</p>

ePRECIDE 2017 (Continued)

Clarified though e-mail correspondence that the trial is double-blind, trial start date and trial completion date

Espinoza 2019

Trial name or title	Metformin for preventing frailty in high-risk older adults
Methods	<p>Type of trial: interventional</p> <p>Allocation: randomised</p> <p>Intervention model: parallel assignment</p> <p>Masking: quadruple (participant, care provider, investigator, outcomes assessor)</p> <p>Primary purpose: prevention</p>
Participants	<p>Condition: older prediabetic people</p> <p>Enrollment: 120</p> <p>Inclusion criteria: men and women; all ethnic groups; age 65 and older; community-dwelling; 2-hour values of 140 mg/dL to 199 mg/dL after an oral glucose load, and no diagnosis of diabetes in the past 12 months; participants must have the following laboratory values: haematocrit \geq 33%, AST $<$ 2 X upper limit of normal, ALT $<$ 2 X upper limit of normal, alkaline phosphatase $<$ 2 X upper limit of normal, normal urinalysis, normal electrolytes, normal platelets, prothrombin time and partial thromboplastin time, and normal renal function for the participant's age (defined by a serum creatinine $<$ 1.5 mg/dL (132.6 mmol/L) in males or $<$ 1.4 mg/dL (123.8 mmol/L) in females and creatinine clearance \geq 60 mL/min)</p> <p>Exclusion criteria: characterised as frail, defined as the presence of 3 or more of: 1) weak hand grip strength, 2) slow walking speed, 3) low physical activity, 4) unintentional weight loss of \geq 10 pounds over the past year, 5) self-reported exhaustion; resident of nursing home or long-term care facility; T2DM; taking drugs known to affect glucose sensitivity; untreated depression or geriatric depression scale score on 15-item scale $>$7; diagnosis of any disabling neurologic disease Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, cerebrovascular accident with residual deficits (muscle weakness or gait disorder), diagnosis of dementia or mini-mental state exam score $<$ 18; history of moderate-severe heart disease (NYHA Classification greater than grade II) or pulmonary disease (dyspnoea on exertion upon climbing one flight of stairs or less; abnormal breath sounds on auscultation); poorly controlled hypertension (SBP $>$170 mmHg, DBP $>$105 mmHg); systemic steroids, anabolic steroids, growth hormone or immunosuppressants within 6 months; chronic inflammatory condition, autoimmune disease, or infectious processes (e.g., active tuberculosis, human immunodeficiency virus, rheumatoid arthritis, systemic lupus erythematosus, hepatitis B or C); active tobacco use (within 6 months); active malignancy, non-skin; disease or condition likely to cause death within 5 years; hypersensitivity to metformin or pioglitazone; donated blood within the last 2 months</p>
Interventions	<p>Intervention: metformin up to 2000 mg</p> <p>Comparator: placebo</p> <p>Duration of intervention: two years</p>
Outcomes	<p>Primary outcomes: frailty composite measure</p> <p>Secondary outcomes: gait speed, grip strength, six minute walk, short physical performance battery, body composition, frailty as defined by a deficit accumulation index</p> <p>Other outcomes: not reported</p>

Espinoza 2019 (Continued)

Starting date	Study start date: April 2016
	Study completion date: October 2022
Contact information	Contact: Alicia Conde, M.A. 210-617-5197
Trial identifier	NCT03222765
Notes	

Ji 2019

Trial name or title	Efficacy of metformin in preventing diabetes in China (ChinaDPP)
Methods	<p>Type of trial: interventional</p> <p>Allocation: randomised</p> <p>Intervention model: parallel assignment</p> <p>Masking: open-label</p> <p>Primary purpose: prevention</p>
Participants	<p>Condition: diagnosis of IGR before the randomisation based on the 1999 WHO diagnostic and classification criteria</p> <p>Enrollment: 1674</p> <p>Inclusion criteria: diagnosis of IGR before the randomisation based on the 1999 WHO diagnostic and classification criteria; 18 ≤ age ≤ 70 years old; not on a treatment of anti-diabetic agents, including Chinese traditional herbs lowering blood glucose for at least six months before screening; male or non-pregnant, non-breastfeeding females, females without birthing plan in next three years; BMI 21 kg/m² ≤ BMI < 32 kg/m²; written informed consent given before any trial-related activities are carried out</p> <p>Exclusion criteria: administration with medications for pre-existed diseases affect glucose metabolism (except thiazide diuretics when its daily dose ≤ 12.5mg); administration with anti-obesity agents (including Chinese traditional medicine) within six months of enrolment and during intervention; administration with three or more than three types antihypertensive drugs; diabetes people (prior history of gestational diabetes will not be excluded); have any of the following cardiovascular conditions within three months prior to the screening visit: acute myocardial infarction, congestive heart failure defined as NYHA class III/IV or left ventricular ejection fraction ≤ 40% or cerebrovascular accident; persistent uncontrolled hypertension (SBP ≥ 160mmHg, or DBP ≥ 100 mmHg); impaired liver function, have obvious clinical signs or symptoms of liver disease, acute or chronic hepatitis, ALT or AST levels ≥ 3 times the upper limit of the reference range at the screening visit; renal dysfunction (GFR < 45mL/minute); people ventilated by ventilator; hypersensitivity to metformin or to any of the excipients such as povidone K 30, magnesium stearate and hypromellose; disease which may cause tissue hypoxia (especially acute disease, or worsening of chronic respiratory disease); acute alcohol intoxication, alcoholism; severe chronic gastrointestinal disease; severe psychiatric illness; cancer requiring treatment in past five years; uncontrolled thyroid diseases; women who are pregnant or breastfeeding; participation in another clinical trial within the past 30 days; other significant disease that in the Investigator's opinion would exclude the person from the trial</p>
Interventions	<p>Intervention: metformin 850 mg twice daily plus standard lifestyle intervention</p> <p>Comparator: standard lifestyle intervention</p>

Ji 2019 (Continued)

	Duration of intervention: 2 years
Outcomes	Primary outcomes: development of T2DM Secondary outcomes: not reported Other outcomes: not reported
Starting date	Study start date: April 25, 2017 Study completion date: December 31, 2022
Contact information	Contact: Guangwei Li, M.D., Ph.D. guangwei_li45@126.com
Trial identifier	NCT03441750
Notes	

JPRN-UMIN000018995

Trial name or title	Metformin therapy for East Asian women with recent gestational diabetes mellitus and glucose abnormalities: a multicenter, randomised, open-label trial
Methods	Type of trial: interventional Allocation: randomised Intervention model: parallel Masking: open-label Primary purpose: not reported
Participants	Condition: women with recent GDM and glucose abnormalities, including IFG, or IGT, or both (IFG, IGT) postpartum Enrollment: 210 Inclusion criteria: women who experienced GDM in a previous singleton pregnancy in the past 5 years; postpartum metabolic abnormalities determined by a 75 g OGTT, inclusive of prior GDM with IFG, IGT, or both (IFG, IGT) postpartum; can respond to the questionnaire in Japanese; over 20 years of age; have a record of clinical data during pregnancy; own the Maternal and Child Health Handbook. Exclusion criteria: currently lactating; planning to conceive in the next two years; a history of diabetes and prior use of metformin or insulin to treat diabetes; a history of lactic acidosis; renal impairment (serum creatinine level \geq 1.2 mg/dL (106 μ mol/L), including dialysis patients); severe liver dysfunction (serum AST and/or ALT level exceeding more than a threefold increase in normal lab values); cardiac failure, cardiac infarction, pulmonary embolism, a high degree of failure in lung function, and hypoxaemia; excessive alcohol intake; malnutrition, or are in a state of starvation or debility, or have pituitary malfunction or adrenal insufficiency; a history of hypersensitivity reaction to metformin or other biguanides; thyroid function that is not controlled by hyperthyroidism (serum free thyroxine levels exceed normal lab values within three months); autoantibody-positive status (e.g. GAD, IA-2), or suspected diabetes mellitus associated with a mutation of mitochondrial DNA, maternally inherited diabetes and deafness, or maturity-onset diabetes of the young; not considered eligible to participate in this study by the attending doctor due to other reasons.
Interventions	Intervention: standard lifestyle intervention

JPRN-UMIN000018995 (Continued)

Comparator: standard lifestyle intervention plus metformin up to 1500 mg per day

Duration of intervention: 24 months

Outcomes

Primary outcomes: period of progression to type 2 diabetes mellitus

Secondary outcomes: change in blood glucose and serum insulin levels determined by a 75 g oral glucose tolerance test (OGTT); change in index of insulin sensitivity (Matsuda index) from baseline and at study end (24 months after initiation of therapy, or the final point to be observed); change in index of insulin resistance (HOMA-IR) from baseline and at study end (24 months after initiation of therapy, or the final point to be observed); change in index of beta-cell function (Disposition index, Insulinogenic index) from baseline and at study end (24 months after initiation of therapy, or the final point to be observed); change in blood pressure, lipid metabolism, and body weight from baseline; improvement to normal glucose tolerance; incidence rate of adverse events

Other outcomes: not stated

Starting date

Study start date: November 2015

Study completion date: not stated

Contact information

Contact: Maki Kawasaki, email: boseinaika@ncchd.go.jp or Naoko Arata, email: boseinaika@ncchd.go.jp

Trial identifier

[JPRN-UMIN000018995](#)

Notes

Nadeau 2014

Trial name or title

RISE adult medication study (RISE adult)

Methods

Type of trial: interventional

Allocation: randomised

Intervention model: parallel

Masking: quadruple

Primary purpose: treatment

Participants

Condition: people with prediabetes and early type 2 diabetes

Enrollment: 267

Inclusion criteria: fasting plasma glucose 95 mg/dL to 125 mg/dL (5.3 mmol/L to 6.9 mmol/L) plus 2-hour glucose \geq 140 mg/dL (7.8 mmol/L) on 75 g OGTT plus HbA1c \leq 7.0%. There is no upper limit for the 2-hour glucose on OGTT; age 20 to 65 years; BMI \geq 25 kg/m² but \leq 50 kg/m²; self-reported diabetes < 1 year in duration; drug naive (no prior to oral glucose lowering agent(s), insulin or other injectable glucose lowering agents)

Exclusion criteria: underlying disease likely to limit life span and/or increase risk of intervention or an underlying condition that is likely to limit ability to participate in outcomes assessment; an underlying disease that affects glucose metabolism other than type 2 diabetes; medications that affect glucose metabolism, or has an underlying condition that is likely to require such medications; active infections; renal disease (serum creatinine >1.4 mg/dL (123.8 μ mol/L) for men; >1.3 mg/dL (114.9 μ mol/L) for women) or serum potassium abnormality (<3.4 or >5.5 mmol/L); anaemia (haemoglobin <11 g/dL (6.8 mmol/L) in women, < 12 g/dL (7.4 mmol/L) in men) or known coagulopathy; cardiovascular disease, including uncontrolled hypertension; participants must be able to

Nadeau 2014 (Continued)

safely tolerate administration of intravenous fluids required during clamp studies; history of conditions that may be precipitated or exacerbated by a study drug: pancreatitis, serum ALT more than 3 times the upper limit of normal, excessive alcohol intake, suboptimally-treated thyroid disease, medullary carcinoma of the thyroid or MEN-2 (in participant or a family history), hypertriglyceridaemia (> 400 mg/dL despite treatment); conditions or behaviours likely to affect the conduct of the RISE Study: unable or unwilling to give informed consent, unable to adequately communicate with clinic staff, another household member is a participant or staff member in RISE, current, recent or anticipated participation in another intervention research project that would interfere with any of the interventions/outcomes in RISE, weight loss of > 5% in past three months for any reason other than postpartum weight loss, participants taking weight loss drugs or using preparations taken for intended weight loss are excluded, likely to move away from participating clinics in next two years, women of childbearing potential who are unwilling to use adequate contraception, current (or anticipated) pregnancy and lactation, major psychiatric disorder that, in the opinion of clinic staff, would impede the conduct of RISE; additional conditions may serve as criteria for exclusion at the discretion of the local site

Interventions	<p>Intervention: metformin up to 2000 mg per day</p> <p>Comparator (1): basal insulin glargine for 3 months followed by open-label metformin for 9 months</p> <p>Comparator (2): placebo, masked to metformin alone</p> <p>Comparator (3): liraglutide + open-label metformin</p> <p>Duration of intervention: 12 months</p>
Outcomes	<p>Primary outcomes: β-cell function measured by hyperglycaemic clamp techniques</p> <p>Secondary outcomes: hyperglycaemic clamp and OGTT measures of β-cell function and glucose tolerance</p> <p>Other outcomes: hyperglycaemic clamp and OGTT measures of β-cell function and glucose tolerance</p>
Starting date	<p>Study start date: April 2013</p> <p>Study completion date: August 2019</p>
Contact information	Contact: Jesse Brown VA medical center, Chicago, Illinois, United States, 60612
Trial identifier	NCT01779362
Notes	Includes people with prediabetes and early type 2 diabetes. Only interesting if a subgroup analysis of the prediabetic population will be performed

NCT01804049

Trial name or title	Metformin and muscle in insulin-resistant older veterans
Methods	<p>Type of study: efficacy study</p> <p>Allocation: randomised</p> <p>Intervention model: parallel assignment</p> <p>Masking: double blind</p> <p>Primary purpose: prevention</p>

NCT01804049 (Continued)

Participants	<p>Condition: prediabetes</p> <p>Enrollment: 120</p> <p>Inclusion criteria: participants with sedentary, weight-stable, ambulatory veterans aged 65 years and older with prediabetes identified with fasting glucose values 100 mg/dL (5.6 mmol/L) or greater but under 126 mg/dL (7.0 mmol/L) with no use of diabetes medications</p> <p>Exclusion criteria: chronic medical conditions affecting muscle mass or function like active non-skin cancer and hypogonadism; Medications affecting muscle mass or function like glucocorticoids and androgen/antiandrogens; contraindications to metformin</p>
Interventions	<p>Intervention: metformin 850 mg orally twice daily</p> <p>Comparator: one placebo capsule by mouth twice daily</p>
Outcomes	<p>Primary outcomes: change in total and appendicular lean mass</p> <p>Secondary outcomes: change in physical performance and muscle histologic characteristics</p>
Starting date	<p>Study start date: February 28, 2013</p> <p>Study completion date: August 2018</p>
Contact information	<p>Michael P Davey, MD PhD</p> <p>VA Portland Health Care System, Portland, OR, USA</p> <p>Tel: 503-273-5125</p> <p>E-mail: michael.davey@va.gov</p>
Trial identifier	NCT01804049
Notes	

NCT02915198

Trial name or title	Investigation of metformin in prediabetes on atherosclerotic cardiovascular outcomes (VA-IMPACT)
Methods	<p>Type of trial: interventional</p> <p>Allocation: randomised</p> <p>Intervention model: parallel</p> <p>Masking: double-blind</p> <p>Primary purpose: treatment</p>
Participants	<p>Condition: people with prediabetes and established atherosclerotic cardiovascular disease</p> <p>Enrollment: 7868</p> <p>Inclusion criteria: prediabetes: this condition is fulfilled by HbA1c of at least 5.7%, but less than 6.5%, or two measurements of fasting plasma glucose (on separate days) of 100 mg/dL to 125 mg/dL (5.6 mmol/L to 6.9 mmol/L), or a 2-hour plasma glucose level of 140 mg/dL to 199 mg/dL (7.8 mmol/L to 11.1 mmol/L) following a 75 g glucose load OGTT. At least one of these criteria must be met in the absence of diabetic treatment; established atherosclerotic cardiovascular disease: qualifying participants must have evidence of atherosclerotic disease in at least one of the following</p>

NCT02915198 (Continued)

vascular beds: coronary, cerebrovascular, or peripheral arterial circulation; renal function: estimated GFR at least 45 mL/min/1.73 m²; informed consent has been fully executed, and participant agrees to study procedures

Exclusion criteria: related to glucometabolic state: treatment with metformin or other antidiabetic medication within 12 months of randomisation, treatment with systemic glucocorticoids within 3 months of randomisation (due to potential effect on plasma glucose and HbA1c levels), fasting plasma glucose 140 mg/dL (7.8 mmol/L) measured between screening and randomisation visits, or any plasma glucose 200 mg/dL (11.1 mmol/L) or HbA1c 7.0% measured within 12 months of randomisation; related to safety or tolerability: metabolic acidosis (total CO₂ below the local laboratory lower limit of normal on most recent blood chemistry panel), current treatment with cimetidine, vandetanib, or a systemic carbonic anhydrase inhibitor (topiramate, acetazolamide, methazolamide, dichlorphenamide, or zonisamide) (use of ophthalmic carbonic anhydrase inhibitors is not exclusionary), cirrhosis, active hepatitis, or jaundice at time of randomisation, or total bilirubin > 2 times upper limit of normal on most recent laboratory study, binge or heavy alcohol consumption within 6 months of randomisation (binge drinking is defined by consumption of 5 or more alcoholic drinks for men or 4 for women within 2 hours, heavy drinking is defined by consumption of 5 or more alcoholic drinks on one occasion, occurring 5 or more times in a month), severe anaemia (haemoglobin < 10 g/dL (6.2 mmol/L)) on screening or most recent laboratory testing, prior history of intolerance to metformin; related to likelihood of non-modifiable events: myocardial infarction, coronary revascularisation procedure (PCI or CABG), or stroke within 1 month of randomisation, uncontrolled hypertension at screening assessment (SBP 180 mm Hg or DBP 110 mm Hg), acute or decompensated congestive heart failure; related to prognosis, reliability, ethics, or data validity: expected survival less than study duration, participants considered to be unable, unwilling, or unreliable to meet protocol requirements, impaired decision-making capacity, defined by any history of dementia or cognitive impairment, concurrent participation in another research study involving a randomised comparison of drug or device treatments, unless specifically excepted by CSP; female participants: pregnant or intent to become pregnant during the trial, lactating, women of childbearing potential who are not using a highly effective method of contraception

Interventions	<p>Intervention: metformin up to 2000 mg per day</p> <p>Comparator: matching placebo</p>
Outcomes	<p>Primary outcomes: time in days to death, non-fatal myocardial infarction, stroke, hospitalisation for unstable angina, or symptom-driven coronary revascularisation</p> <p>Secondary outcomes: time in days to cardiovascular outcomes, time in days to oncologic outcome, time in days to diabetes outcome</p> <p>Other outcomes: not stated</p>
Starting date	<p>Study start date: February 2019</p> <p>Study completion date: August 2024</p>
Contact information	<p>Contact: Gregory G. Schwartz, PhD MD, telephone: (720) 723-6070, email: Gregory.Schwartz@va.gov</p>
Trial identifier	<p>NCT02915198</p>
Notes	

NCT02969798

Trial name or title	Pre-diabetes in participants with impaired fasting glucose (IFG) and impaired glucose tolerance (IGT)
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NCT02969798 (Continued)

Methods	<p>Type of trial: efficacy trial</p> <p>Allocation: randomised</p> <p>Intervention model: cross-over assignment</p> <p>Masking: open-label</p> <p>Primary purpose: treatment</p>
Participants	<p>Condition: IGT and IFG</p> <p>NGT participants will serve as controls and will be matched in age, gender, ethnicity and BMI to IGT and IFG participants</p> <p>Enrolment: 700</p> <p>Inclusion criteria: age 18 to 65 years; FPG < 100 mg/dL (5.6 mmol/L) and 2-h PG < 140 mg/dL (7.8 mmol/L); BMI 24 kg/m²; to 40 kg/m²; stable body weight (\pm 4 pounds (1.8 kg)) over the preceding 3 months; no evidence of major organ system disease as determined by physical examination, history and screening laboratory data; women of childbearing potential with a negative pregnancy test at screening and treatment visits, using contraception for the duration of participation in the study (i.e. until follow-up 7 to 14 days after last dose) (oral contraceptive, injectable progesterone, subdermal implant, spermicidal foam/gel/film/cream/suppository, diaphragm with spermicide, copper or hormonal-containing IUD, vasectomised male partner > 6 month predosing); signed and dated informed consent document indicating that participant has been informed of all pertinent aspects of study; willing and able to comply with scheduled visits, treatment, laboratory tests and study procedures</p> <p>Exclusion criteria: recent (i.e. within 3 months prior to screening) evidence or medical history of unstable concurrent disease such as: documented evidence or history of clinically significant haematological, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, immunological or clinically significant neurological disease; family history of diabetes in a first-degree relative; BMI < 24 or > 40 kg/m²; unstable body weight (change \pm 4 pounds (1.8 kg) over the preceding 3 months); participating in an excessively heavy exercise programme; feeding/sleeping schedule different from a daytime feeding/night-time sleeping schedule; receiving medications known to alter glucose metabolism (with the exception of metformin or pioglitazone, or both) or which effect brain neurosynaptic function; evidence of major organ system disease as determined by physical examination, history and screening laboratory data; pregnant or unwilling to use contraception during study; blood donation of approximately 1 pint (500 mL) within 8 weeks prior to screening; other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in judgement of investigator, would make participant inappropriate for entry into study; people haematuria; evidence or prior history of heart failure; family history of pancreatic, bladder and breast cancer; history of pancreatitis; estimated GFR < 60 \pm 5 mL/minute/1.73 m²; elevated serum creatinine (> 1.5 mg/dL for men/1.4 mg/dL for women); history of orthostatic hypotension (> 15 mmHg/10 mmHg); liver enzymes > 3-fold above upper normal limit; history of hypersensitivity to pioglitazone, dapagliflozin or saxagliptin.</p>
Interventions	<p>Intervention: saxagliptin 5 mg/day</p> <p>Comparator (1): dapagliflozin 100 mg/day</p> <p>Comparator (2): pioglitazone 30 mg/day</p> <p>Comparator (3): metformin 200 mg/day</p> <p>The trial will randomise participants exclusively with IGT to 1 treatment group; participants exclusively with IFG to 1 treatment group and participants with IGT plus IFG to 1 treatment group</p> <p>Duration of intervention: 24 months</p>

NCT02969798 (Continued)

Outcomes	<p>Primary outcomes: β-cell function, insulin sensitivity and glucose tolerance status in people with isolated IGT; β-cell function, insulin sensitivity and glucose tolerance status in people with isolated IFG; β-cell function, insulin sensitivity and glucose tolerance status in people with IGT plus IFG</p> <p>Secondary outcomes: not stated</p> <p>Other outcomes: not stated</p>
Starting date	<p>Trial start date: January 2014</p> <p>Trial completion date: July 2020</p>
Contact information	Responsible party/principal investigator: Ralph A DeFronzo, The University of Texas Health Science Center at San Antonio
Trial identifier	NCT02969798
Notes	There is a control arm with participants with NGT - these will not be included in updates of our review

NCT03194009

Trial name or title	Diabetes prevention via exercise, nutrition and treatment (PRuDENTE)
Methods	<p>Type of trial: interventional</p> <p>Allocation: randomised</p> <p>Intervention model: parallel assignment</p> <p>Masking: open-label</p> <p>Primary purpose: prevention</p>
Participants	<p>Condition: adults with FPG between 100 mg/dL and 125 mg/dL (5.6 mmol/L to 6.9 mmol/L)</p> <p>Enrollment: 3060</p> <p>Inclusion criteria: having received primary care in the chosen health centre (ideally two or more visits to that clinic in the prior year); subscribers to "Seguro Popular" (Mexican national health insurance); BMI \geq 30 kg/m²; results of FPG with values for prediabetes diagnosis (glucose between 100 mg/dL and 125 mg/dL (5.6 mmol/L to 6.9 mmol/L))</p> <p>Exclusion criteria: renal insufficiency (GFR < 30 mL/minute); known hepatic impairment or altered liver enzymes (AST or ALT three times above normal values; active alcoholism or drug addiction; allergies or previous known intolerance to exercise or metformin; current pregnancy; plans to leave the area in the next three years; previous diagnosis of T2DM</p>
Interventions	<p>Intervention: metformin plus lifestyle modifications recommendations (physical activity and diet)</p> <p>Comparator: lifestyle modifications recommendations (physical activity and diet)</p> <p>Duration of intervention: three years</p>
Outcomes	<p>Primary outcomes: diabetes measured by HbA1c and fasting blood glucose; lifestyle modifications by decreasing adiposity indicators; caloric intake; physical activity</p> <p>Secondary outcomes: implementation process outcomes at the clinic level; implementation process outcomes patient level; cost-utility of metformin</p>

NCT03194009 (Continued)

	Other outcomes: not reported
Starting date	Study start date: August 10, 2017 Study completion date: December 31, 2022
Contact information	Contact: Luz María Sánchez-Romero, MD, PhD luz.sanchez@insp.mx Alberto Gallardo, MD albgallardo@yahoo.com.mx
Trial identifier	NCT03194009
Notes	

Rhee 2019

Trial name or title	Hospital-based diabetes prevention study in Korea: A prospective, multicenter, randomised, open-label, controlled study
Methods	Type of trial: interventional Allocation: randomised Intervention model: parallel Masking: open-label Primary purpose: prevention
Participants	Condition: IFG, IGT Enrollment: 744 Inclusion criteria: 30 < age < 71; BMI ≥ 23 kg/m ² ; 75 g OGTT 2 hours after the test blood glucose 140 mg/dL ~ 199 mg/dL (7.8 mmol/L ~ 11.1 mmol/L) or fasting blood sugar 110 mg/dL ~ 125 mg/dL (6.1 mmol/L ~ 6.9 mmol/L) or HbA1c 5.7% ~ 6.4% Exclusion criteria: diagnosed with diabetes mellitus except for maternity period or having drugs for diabetes mellitus; type 2 diabetes mellitus; fasting glucose ≥ 126 mg/dL (7.0 mmol/L); 75 g OGTT 2 hours after the blood glucose ≥ 200 mg/dL (11.1 mmol/L); HbA1c ≥ 6.5%; short life expectancy; history of severe cardiovascular disease within the last 6 months (cerebral haemorrhage, stroke, myocardial infarction, angina pectoris, heart failure, etc.); SBP >180 mmHg or DBP >105 mmHg; aortic stenosis; left bundle branch block or third degree AV block; diagnosed and treated for malignant tumours including leukaemia and lymphoma within the last 5 years; abnormal renal function (creatinine ≥ 1.4 mg/dL (123.8 mmol/L) (male) or ≥ 1.3 mg/dL (114.9 mmol/L) (female) or urine protein ≥ 2 +); anaemia (haematocrit < 36% ((male) or >> 33% (female)); cirrhosis or chronic active hepatitis (AST/ALT > 3 UNL); acute gastrointestinal disease (pancreatitis, infectious intestinal disease); surgery within the last 3 to 6 months or just after the surgery; chronic infection (HIV, active tuberculosis, etc.); pulmonary patients who rely on oxygen or daily bronchodilators; judged to be able to influence the clinical trial by investigator; can not communicate; psychiatric or cognitive impairment that may affect the compliance of the clinical trial; do not agree to the treatment group allocation by random assignment; participate in other studies that may interfere with the clinical trial; lost weight by more than 10% during the past 6 months, excluding weight loss after giving birth; can not have normal walking or exercise; currently pregnant or who are within the last 3 months after giving birth; planning pregnancy during the clinical trial period; have a history of drug and alcohol abuse (acute, chronic) within the last 2 years; not appropriate or unreliable for clinical trials at the discretion of the tester; taking medication or medical condition that may affect the diagnosis of diabetes (thiazide diuretics, systemic beta blockers, taking Niacin for the treatment of neutropenic

Rhee 2019 (Continued)

depression, possibility of taking or injecting a systemic steroid preparation, taking a serotonin reuptake inhibitor (SSRI) for weight loss purpose, taking medicine for weight loss; hormone status is not appropriate during thyroid hormone replacement therapy (TSH abnormal range) (If thyroid hormone therapy is stable for more than 3 months and TSH is normal, the participant can participate in); other endocrine diseases (e.g. Cushing's syndrome, acromegaly); during treatment, fasting plasma triglyceride > 600 mg/dL (6.8 mmol/L)

Interventions	Intervention: life style modification Comparator (1): conventional management Comparator (2): metformin up to 1000 mg per day Duration of intervention: 36 months
Outcomes	Primary outcomes: cumulative incidence of diabetes mellitus after randomisation Secondary outcomes: change on HbA1c, fasting glucose and HOMA2%B Other outcomes: not stated
Starting date	Study start date: November 2016 Study completion date: November 2020
Contact information	Contact: Jeong-Taek Woo, email: jtwoomd@khmc.or.kr or Sang Youl Rhee, email: bard95@han-mail.net
Trial identifier	NCT02981121
Notes	

2hPG: 2-hour glucose after an OGTT; **AST:** aspartate amino transferase; **ALT:** alanine amino transferase; **BMI:** body mass index; **CABG:** coronary artery bypass graft; **DBP:** diastolic blood pressure; **DNA:** deoxyribonucleic acid; **ETDRS:** Early Treatment Diabetic Retinopathy Study; **FPG:** fasting plasma glucose; **GAD:** glutamate decarboxylase; **GDM:** gestational diabetes mellitus; **GFR:** glomerular filtration rate; **HbA1c:** glycosylated haemoglobin A1c; **IA-2:** insulin antibodies - 2; **IFG:** impaired fasting glucose; **IGR:** impaired glucose regulation; **IGT:** impaired glucose tolerance; **NGT:** normal glucose tolerance; **NYHA:** New York Heart Association; **OGTT:** oral glucose tolerance test; **PCI:** percutaneous coronary intervention; **SBP:** systolic blood pressure; **SD:** standard deviation; **TSH:** thyroid stimulating hormone; **T2DM** type 2 diabetes mellitus.

blood glucose mg/dL converted to mmol/L (via <https://www.diabetes.co.uk/blood-sugar-converter.html>)

creatinine mg/dL converted to μ mol/L (via <http://www.endmemo.com/medical/unitconvert/Creatinine.php>)

haemoglobin g/dL converted to mmol/L (via <http://unitslab.com/node/7>)

pounds converted to kg (via <https://www.convertunits.com/from/pounds/to/kg>)

triglycerides mg/dL converted to mmol/L (via <http://www.endmemo.com/medical/unitconvert/Triglycerides.php>)

DATA AND ANALYSES

Comparison 1. Metformin versus placebo or diet and exercise

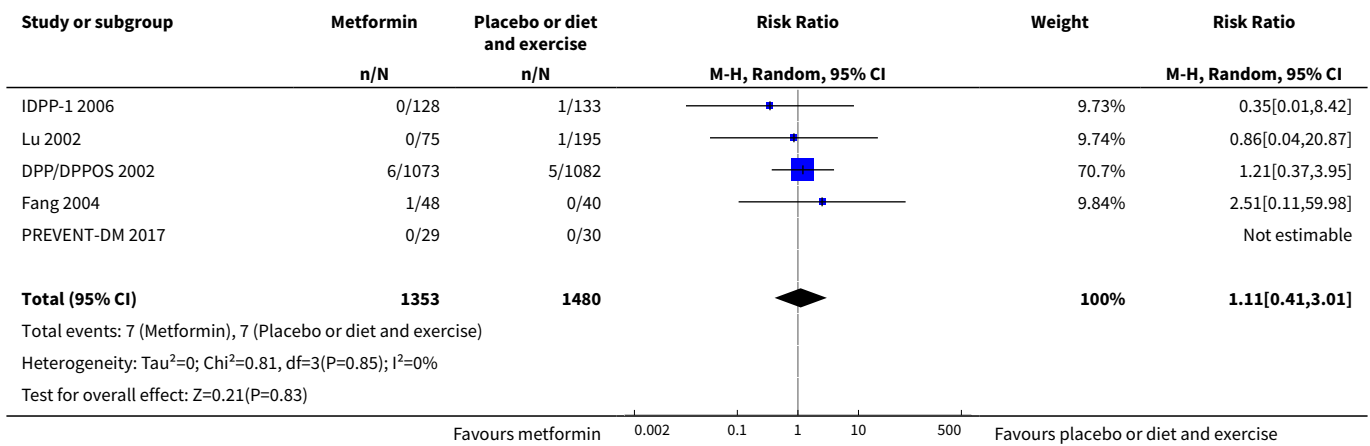
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	5	2833	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.41, 3.01]
2 Incidence of type 2 diabetes	12	3632	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.38, 0.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Incidence of type 2 diabetes (blinded vs open-label)	12	3632	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.38, 0.65]
3.1 Participants blinded	2	2240	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.64, 0.86]
3.2 Open-label	10	1392	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.27, 0.59]
4 Incidence of type 2 diabetes (duration of the intervention)	12	3632	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.38, 0.65]
4.1 Duration of the intervention less than 2 years	4	296	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.14, 0.66]
4.2 Duration of the intervention 2 years or more	8	3336	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.40, 0.71]
5 Incidence of type 2 diabetes (ethnicity)	12	3632	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.38, 0.65]
5.1 mainly White	1	2155	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.65, 0.87]
5.2 mainly Asian	10	1418	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.28, 0.59]
5.3 Other	1	59	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.13]
6 Non-serious adverse events	2	285	Risk Ratio (M-H, Random, 95% CI)	3.86 [0.18, 83.36]
7 2-hr glucose values	13	3346	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.26, -0.46]
8 2-hr glucose values (blinded vs open-label)	13	3346	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.26, -0.46]
8.1 Participants blinded	4	2032	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.86, 0.33]
8.2 Open-label	9	1314	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.35, -0.71]
9 2-hr glucose values (duration of intervention)	13	3346	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.26, -0.46]
9.1 Duration of intervention less than 2 years	4	286	Mean Difference (IV, Random, 95% CI)	-1.37 [-1.91, -0.82]
9.2 Duration of intervention 2 years or more	9	3060	Mean Difference (IV, Random, 95% CI)	-0.75 [-1.18, -0.33]
10 2-r glucose values (ethnicity)	13	3346	Mean Difference (IV, Random, 95% CI)	-0.86 [-1.26, -0.46]
10.1 Mainly White	1	1856	Mean Difference (IV, Random, 95% CI)	0.0 [-0.17, 0.17]

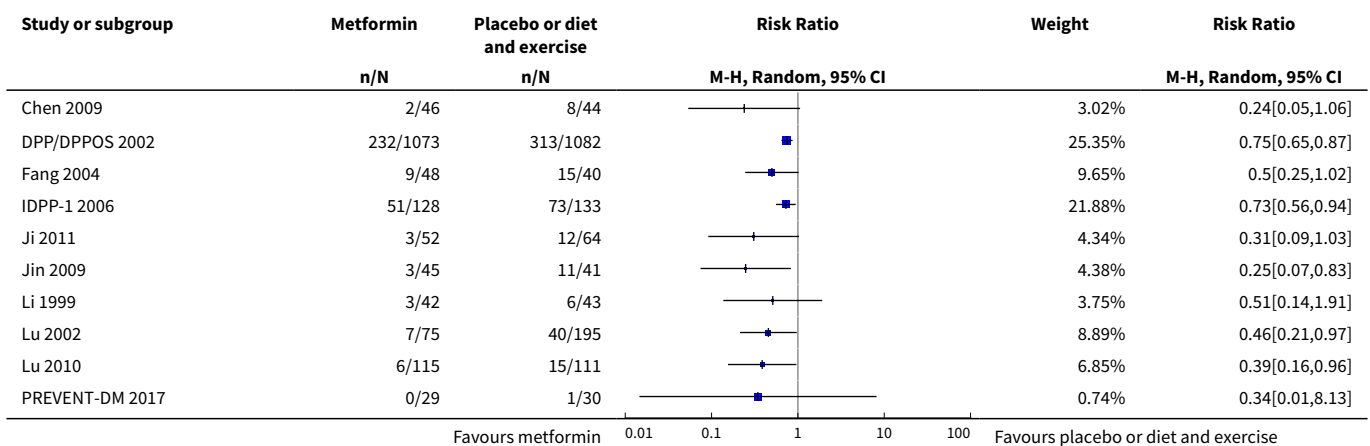
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Mainly Asian	10	1384	Mean Difference (IV, Random, 95% CI)	-1.05 [-1.35, -0.75]
10.3 Other	2	106	Mean Difference (IV, Random, 95% CI)	0.05 [-0.69, 0.79]
11 HbA1c (blinded vs open-label)	6	2467	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.22, 0.05]
11.1 Participants blinded	2	1926	Mean Difference (IV, Random, 95% CI)	0.0 [-0.04, 0.04]
11.2 Open-label	4	541	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.77, 0.08]
12 HbA1c (duration of intervention)	6	2467	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.22, 0.05]
12.1 Duration of intervention less than 2 years	3	269	Mean Difference (IV, Random, 95% CI)	-0.15 [-0.50, 0.21]
12.2 Duration of intervention 2 years or more	3	2198	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.75, 0.22]
13 HbA1c (ethnicity)	6	2467	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.22, 0.05]
13.1 Mainly White	1	1856	Mean Difference (IV, Random, 95% CI)	0.0 [-0.04, 0.04]
13.2 Mainly Asian	4	556	Mean Difference (IV, Random, 95% CI)	-0.45 [-0.74, -0.16]
13.3 Other	1	55	Mean Difference (IV, Random, 95% CI)	0.0 [-0.11, 0.11]
14 Fasting plasma glucose	15	3546	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.42, -0.13]
15 Fasting plasma glucose (blinded vs open-label)	15	3546	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.42, -0.13]
15.1 Participants blinded	4	2037	Mean Difference (IV, Random, 95% CI)	-0.51 [-0.94, -0.09]
15.2 Open-label	11	1509	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.42, -0.03]
16 Fasting plasma glucose (duration of the intervention)	15	3546	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.42, -0.13]
16.1 Duration of the intervention less than 2 years	6	485	Mean Difference (IV, Random, 95% CI)	-0.51 [-0.89, -0.13]

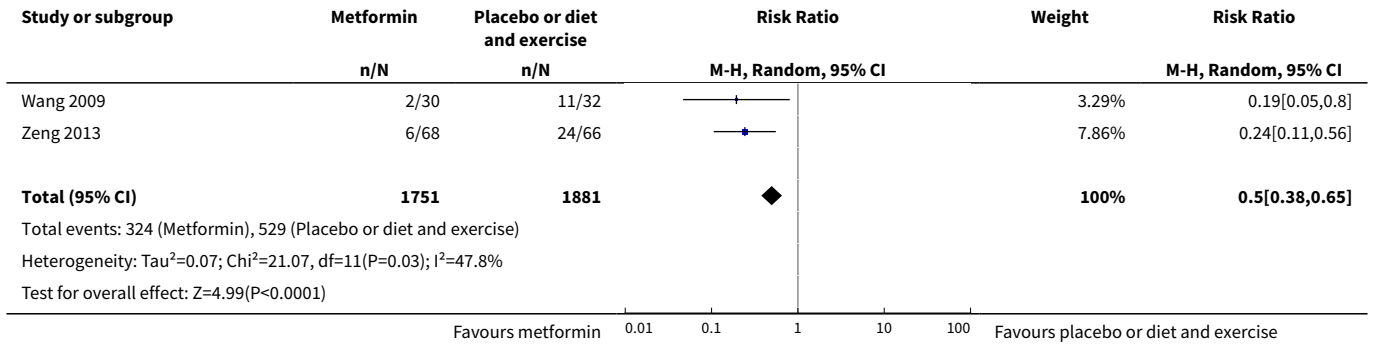
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.2 Duration of the intervention 2 years or more	9	3061	Mean Difference (IV, Random, 95% CI)	-0.19 [-0.35, -0.02]
17 Fasting plasma glucose (ethnicity)	15	3546	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.42, -0.13]
17.1 Mainly White	1	1861	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.39, -0.21]
17.2 Mainly Asian	11	1524	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.51, -0.11]
17.3 Other	3	161	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.49, 0.22]

Analysis 1.1. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 1 All-cause mortality.

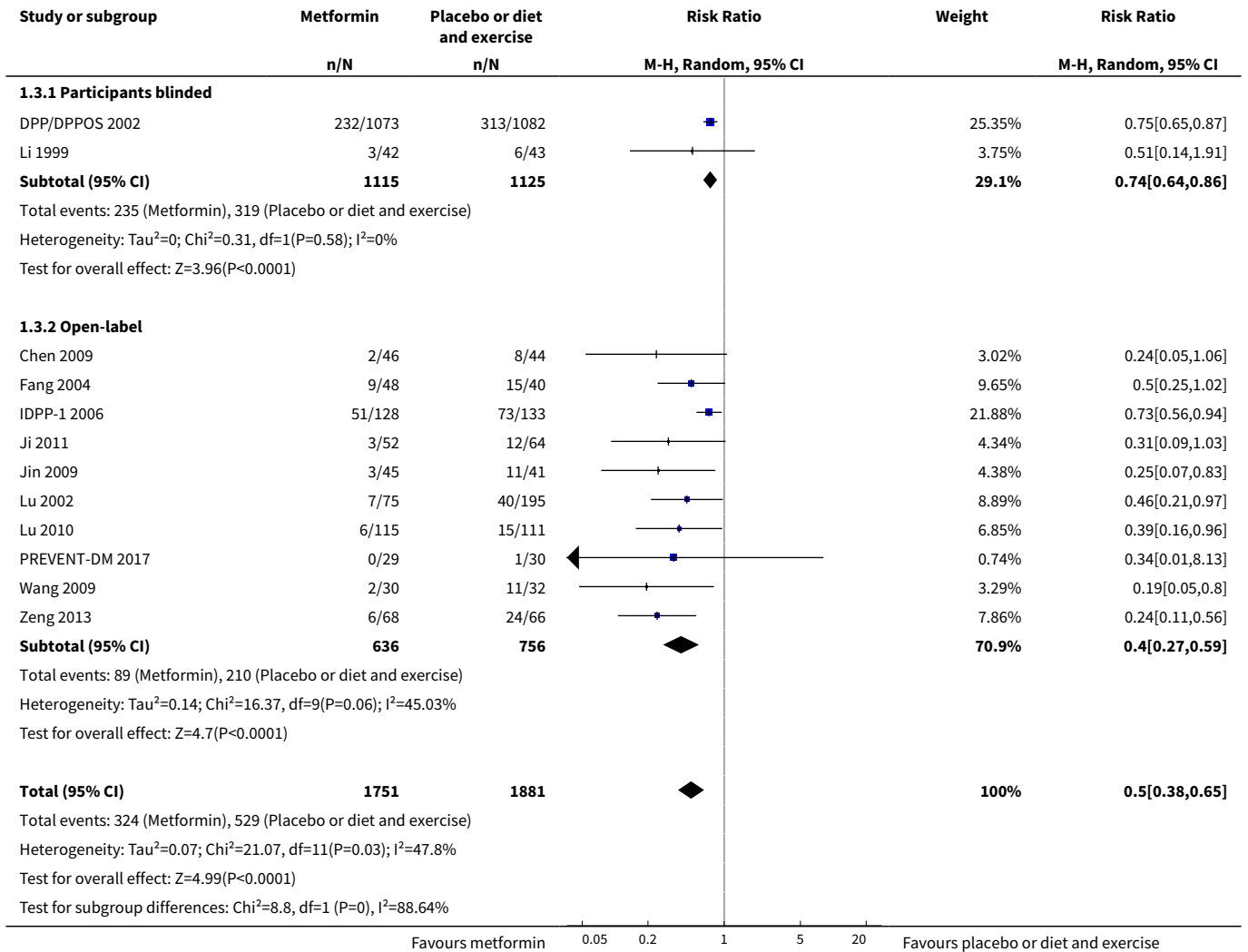


Analysis 1.2. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 2 Incidence of type 2 diabetes.

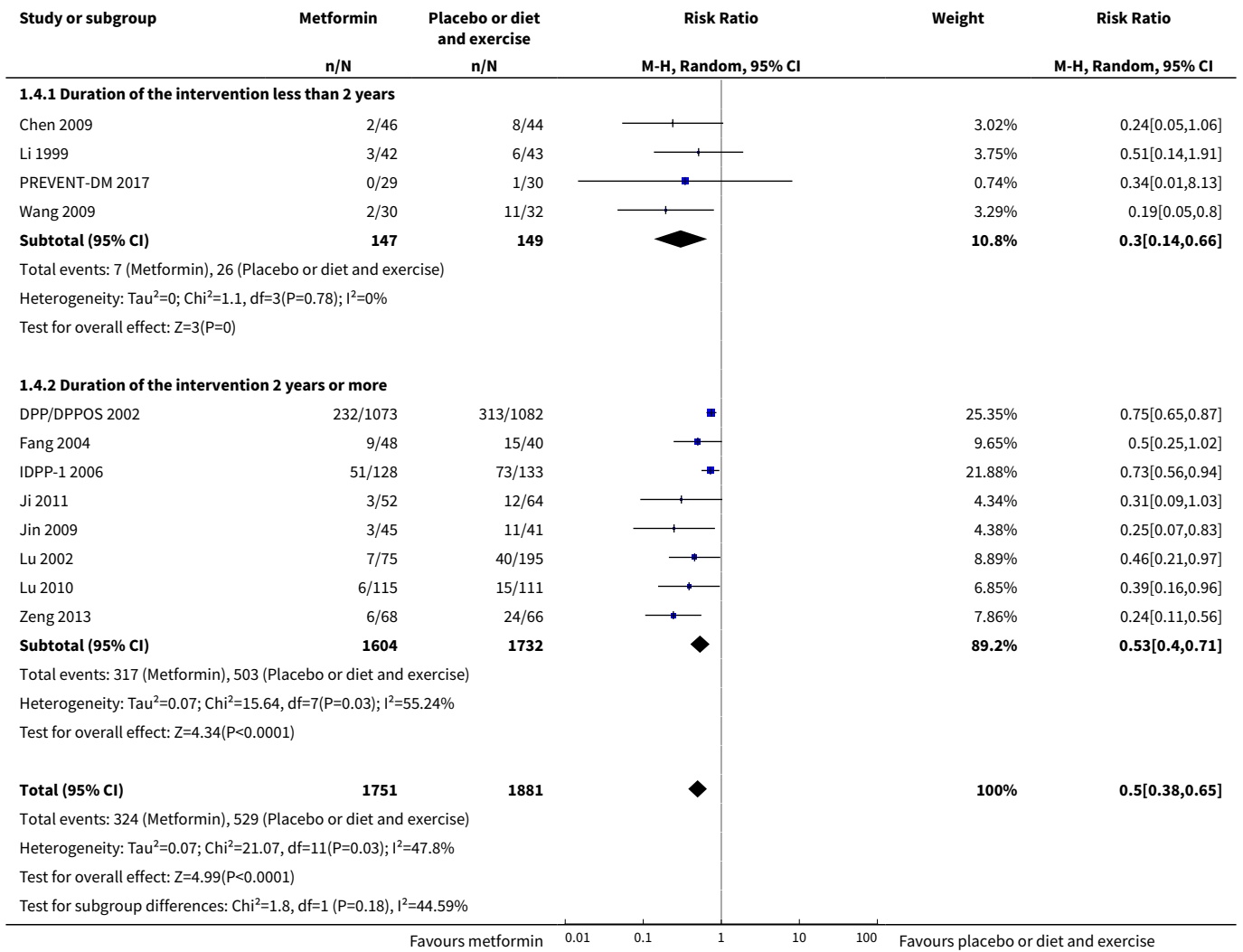




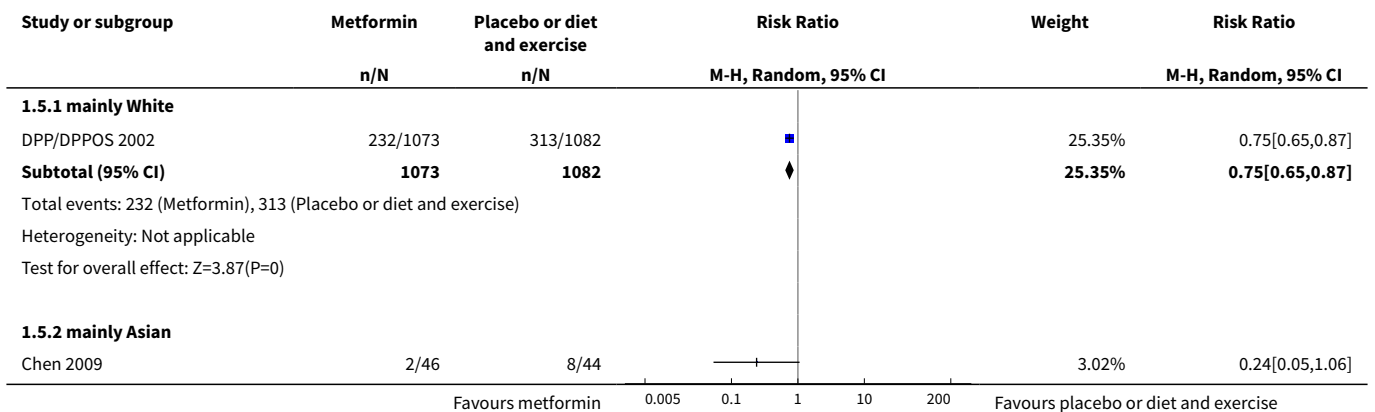
Analysis 1.3. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 3 Incidence of type 2 diabetes (blinded vs open-label).

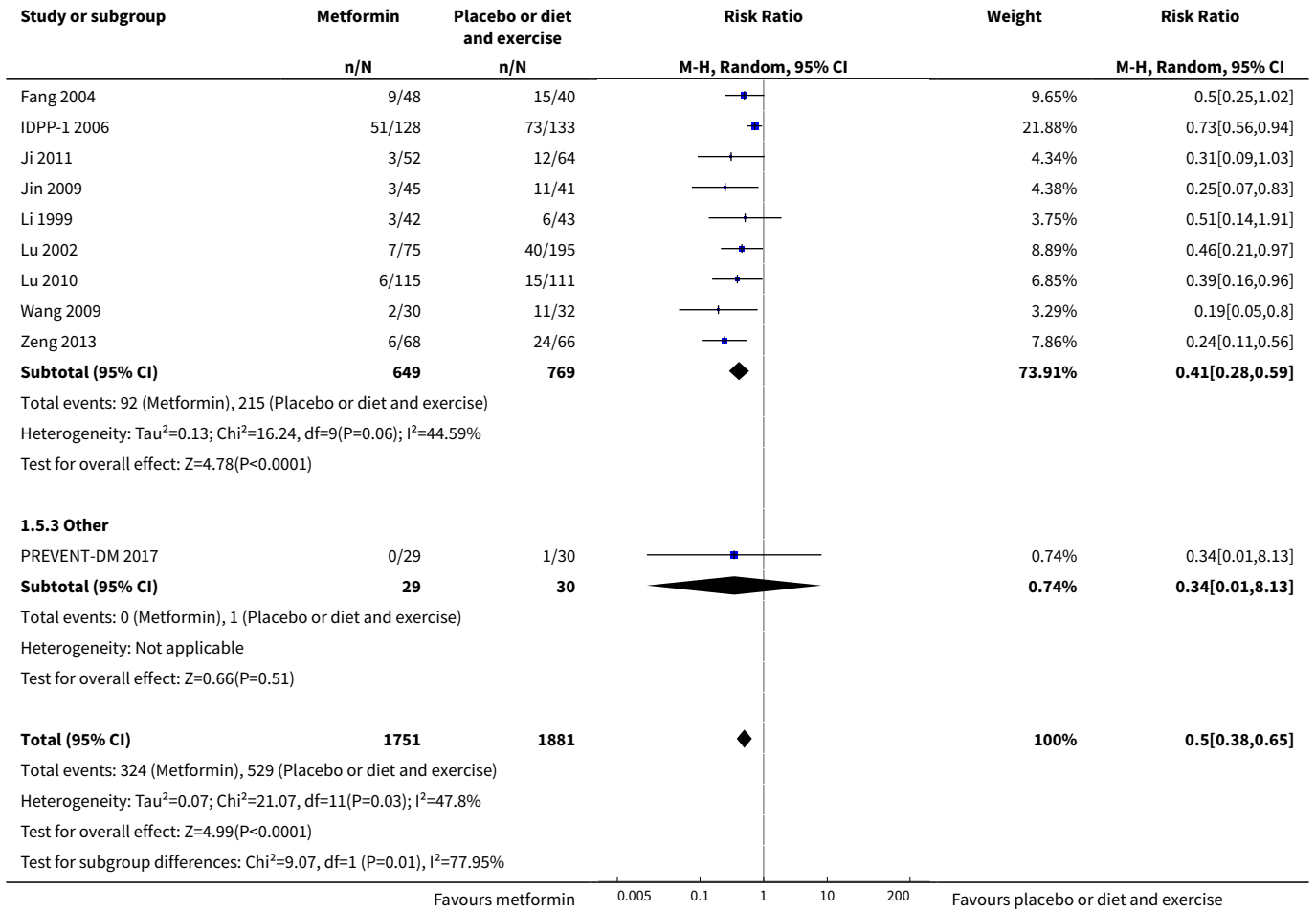


Analysis 1.4. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 4 Incidence of type 2 diabetes (duration of the intervention).

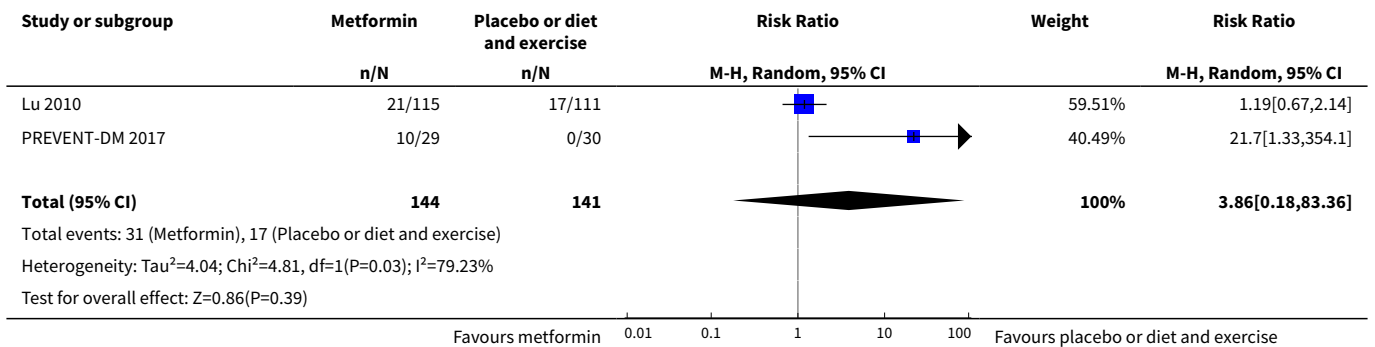


Analysis 1.5. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 5 Incidence of type 2 diabetes (ethnicity).

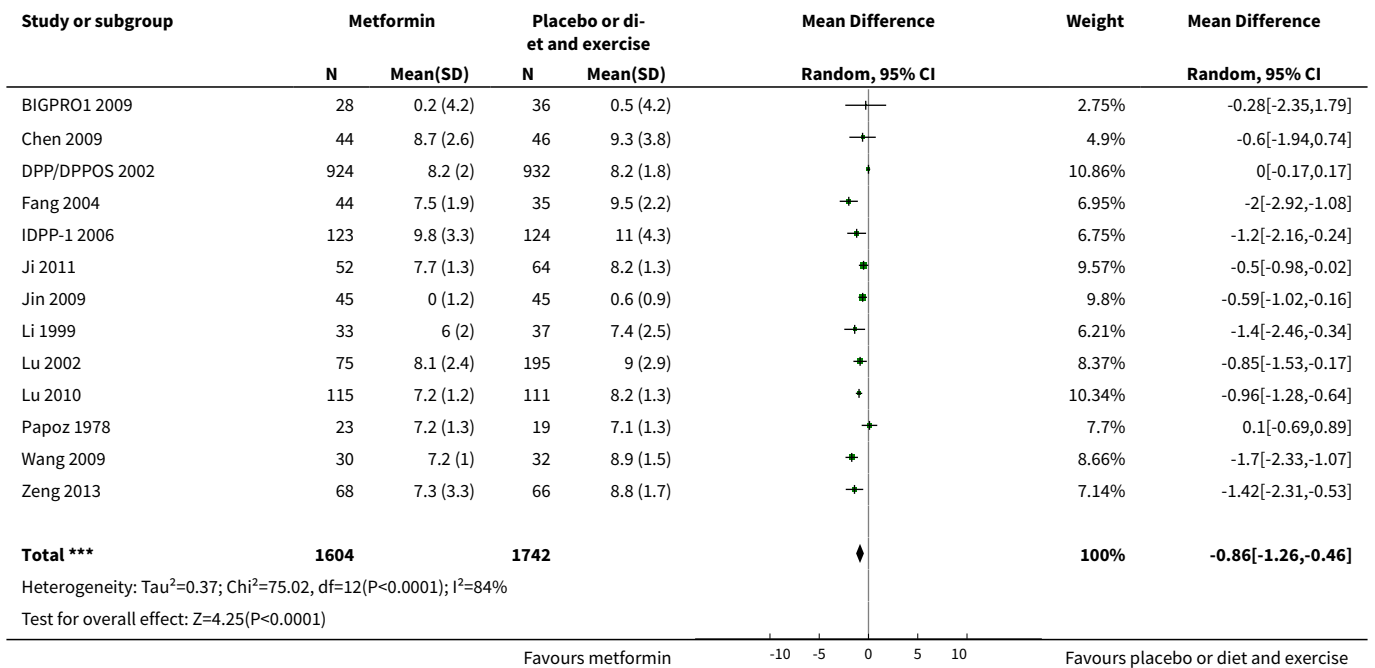




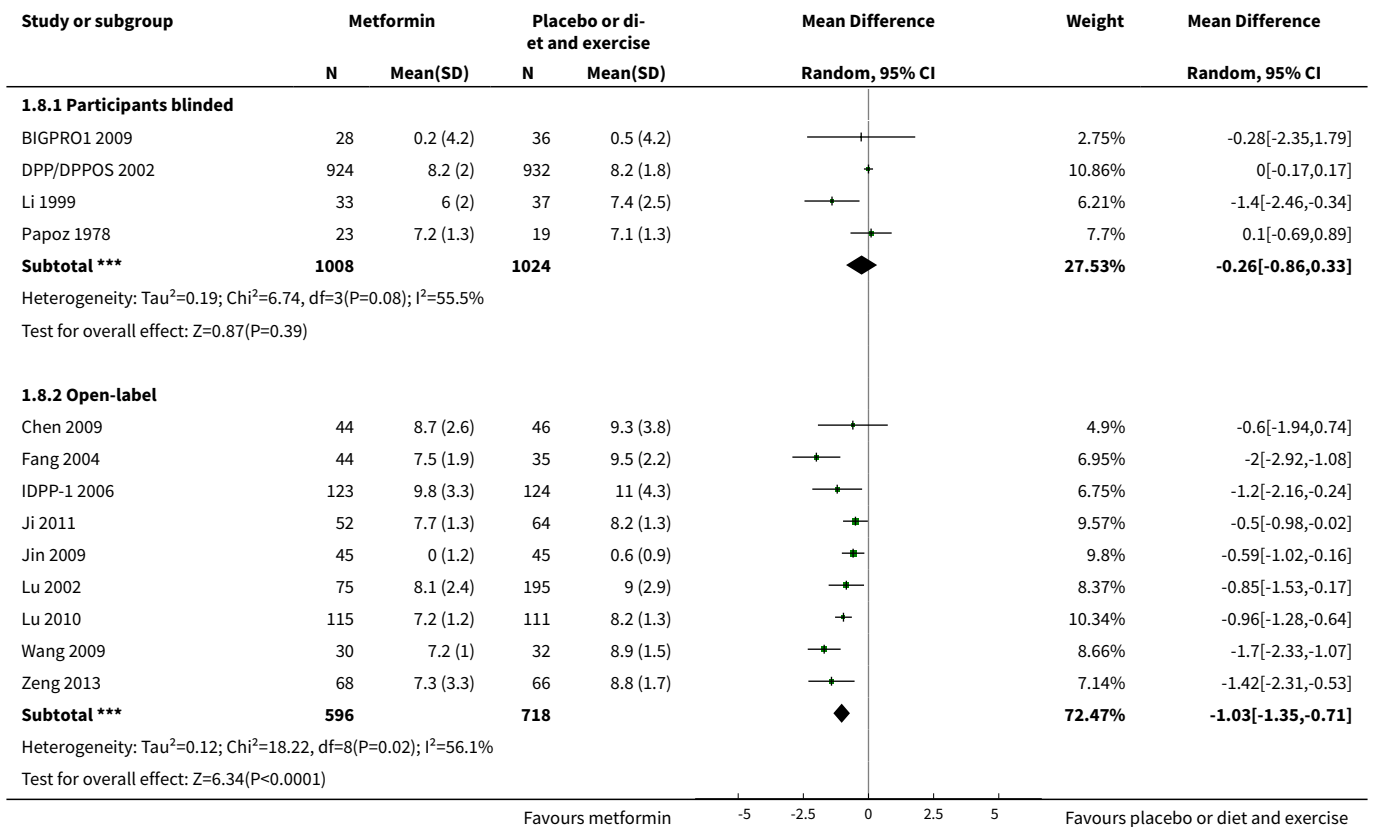
Analysis 1.6. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 6 Non-serious adverse events.

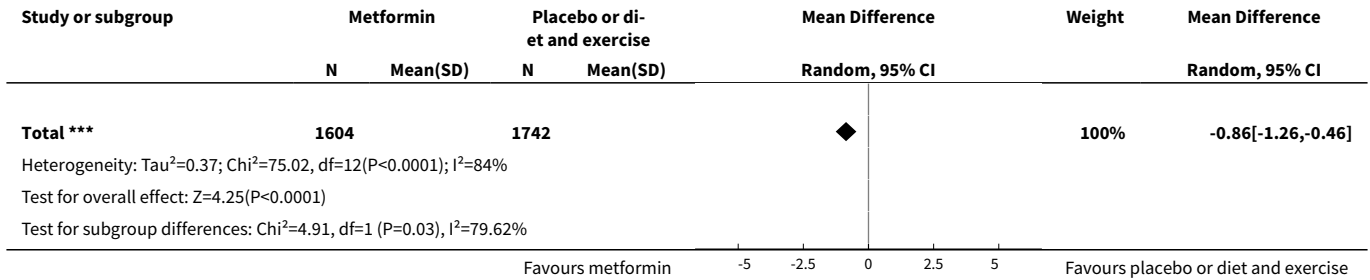


Analysis 1.7. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 7 2-hr glucose values.

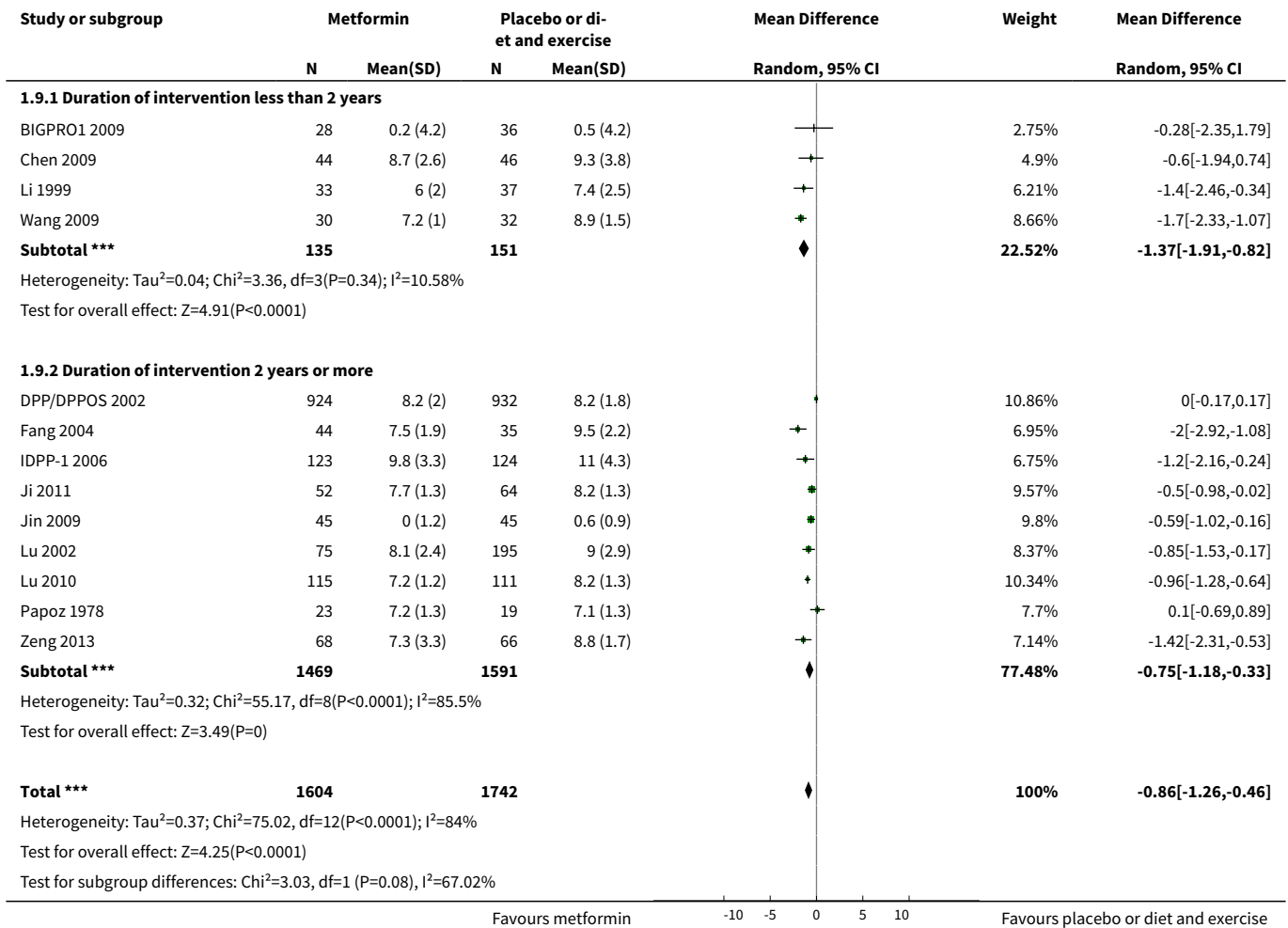


Analysis 1.8. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 8 2-hr glucose values (blinded vs open-label).

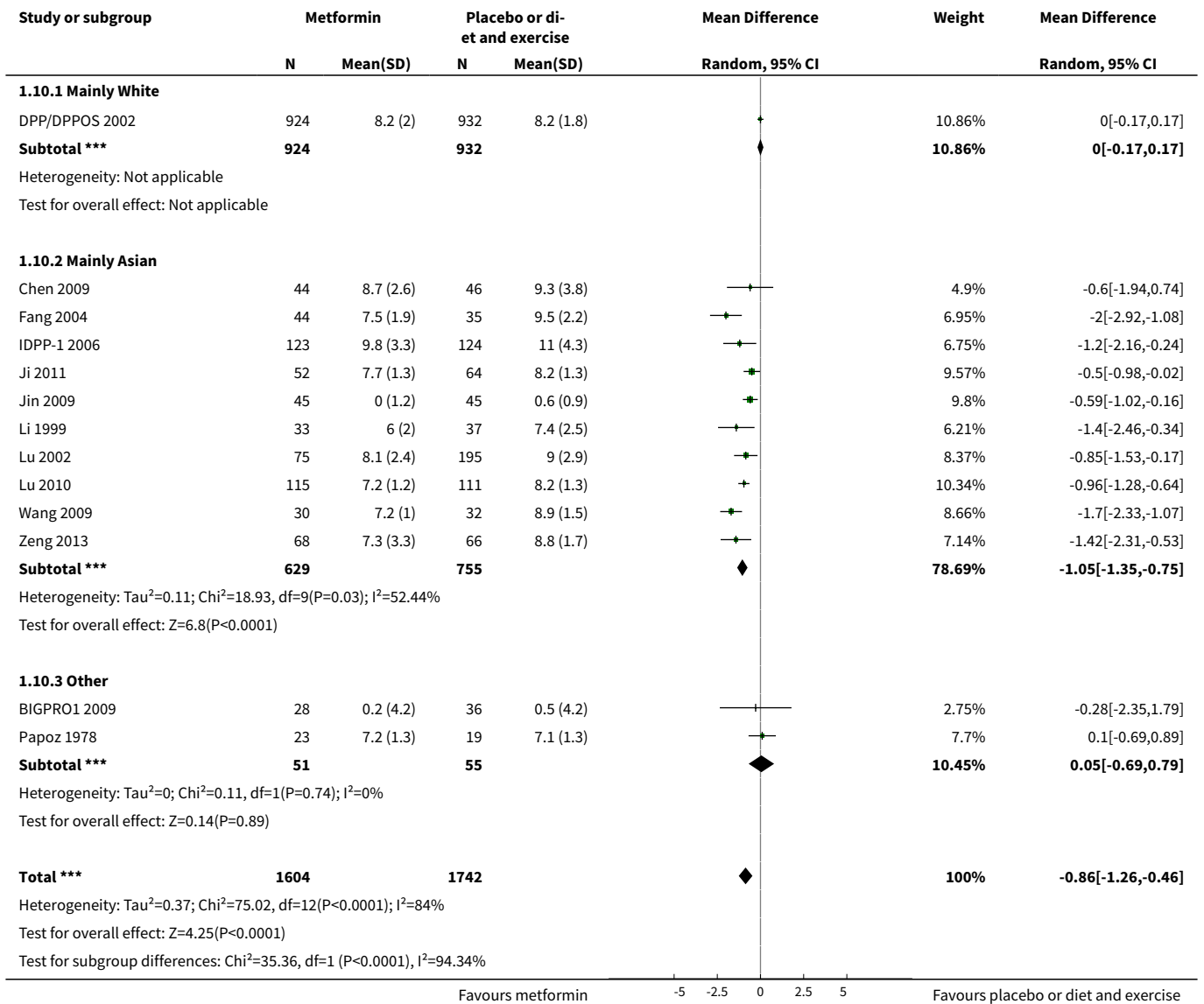




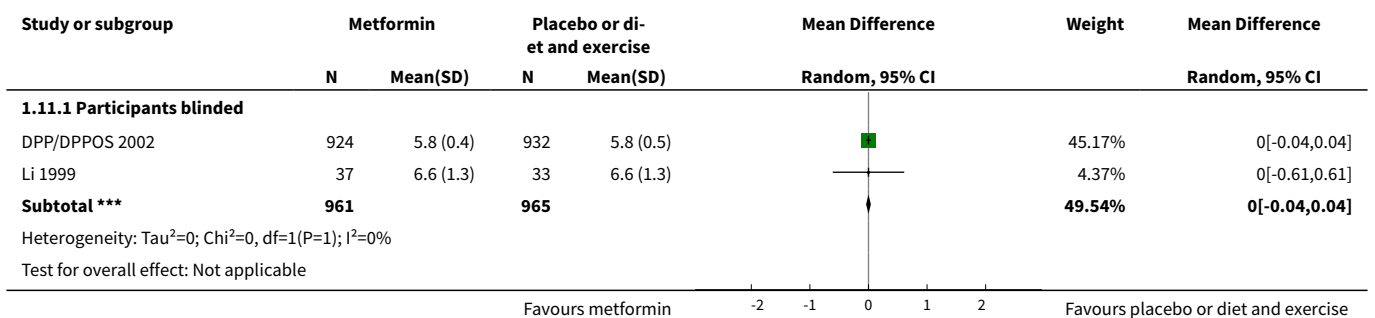
Analysis 1.9. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 9 2-hr glucose values (duration of intervention).

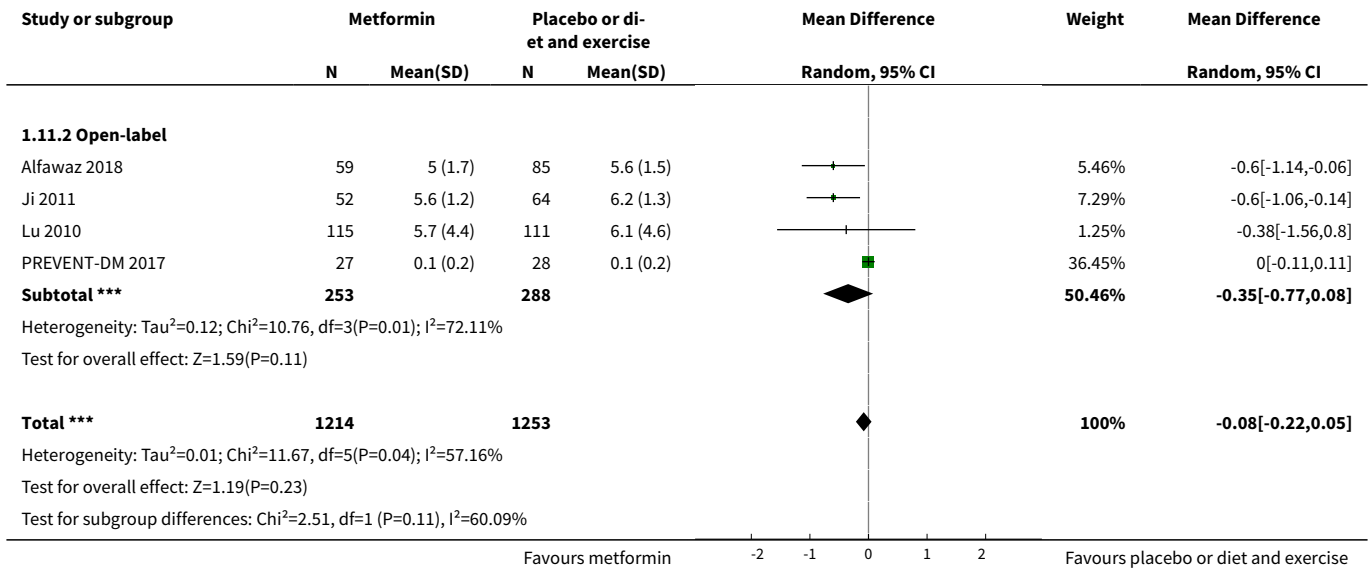


Analysis 1.10. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 10 2-r glucose values (ethnicity).

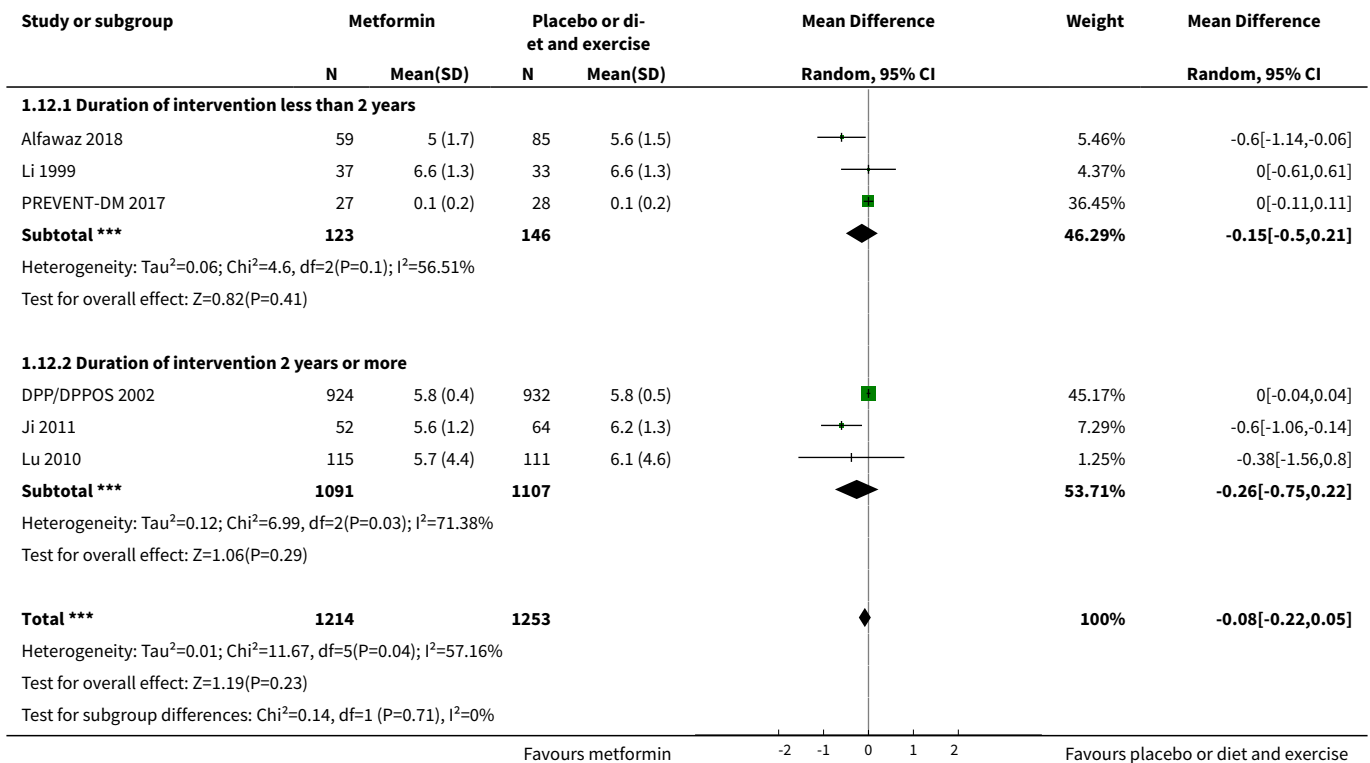


Analysis 1.11. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 11 HbA1c (blinded vs open-label).

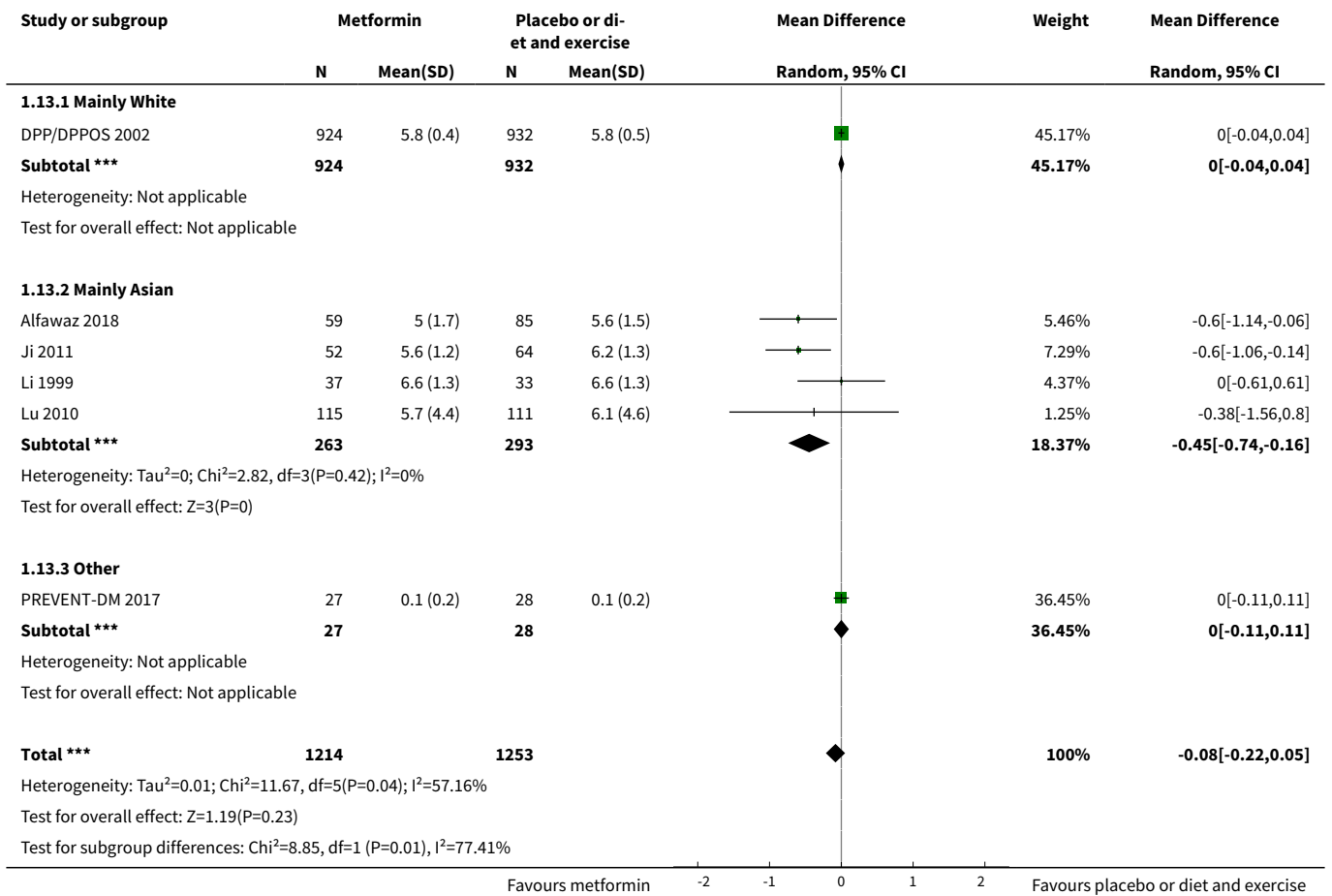




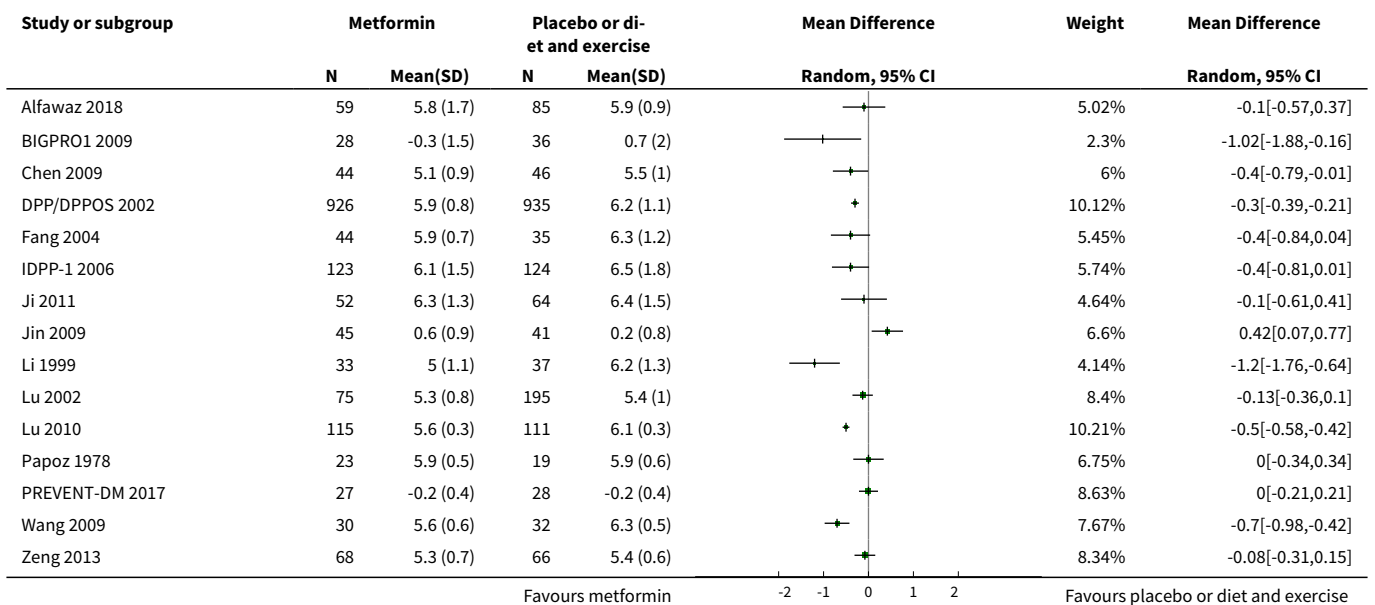
Analysis 1.12. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 12 HbA1c (duration of intervention).

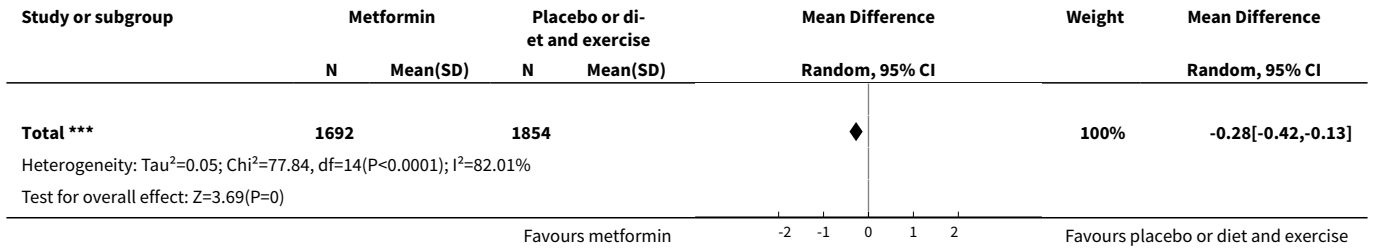


Analysis 1.13. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 13 HbA1c (ethnicity).

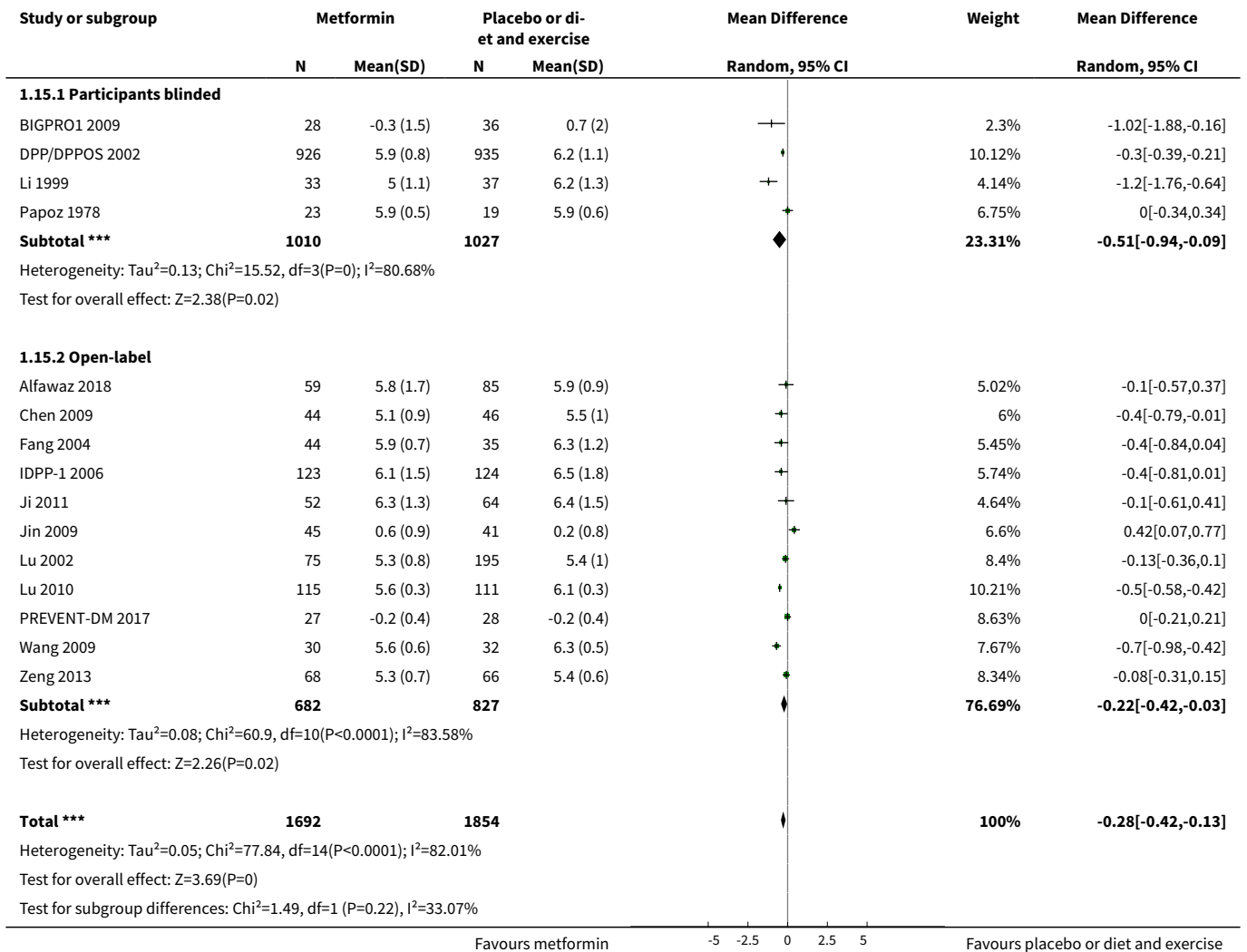


Analysis 1.14. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 14 Fasting plasma glucose.

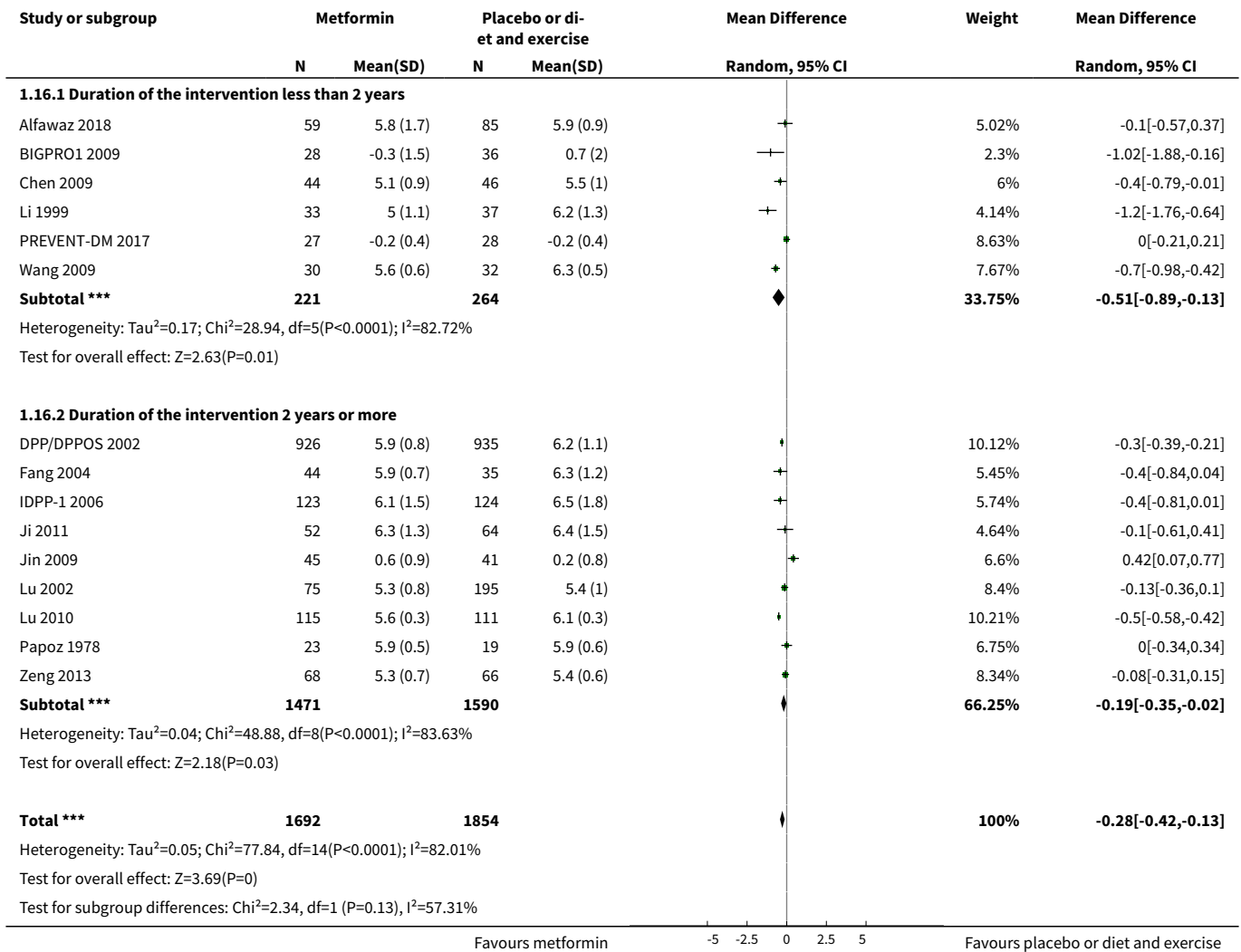




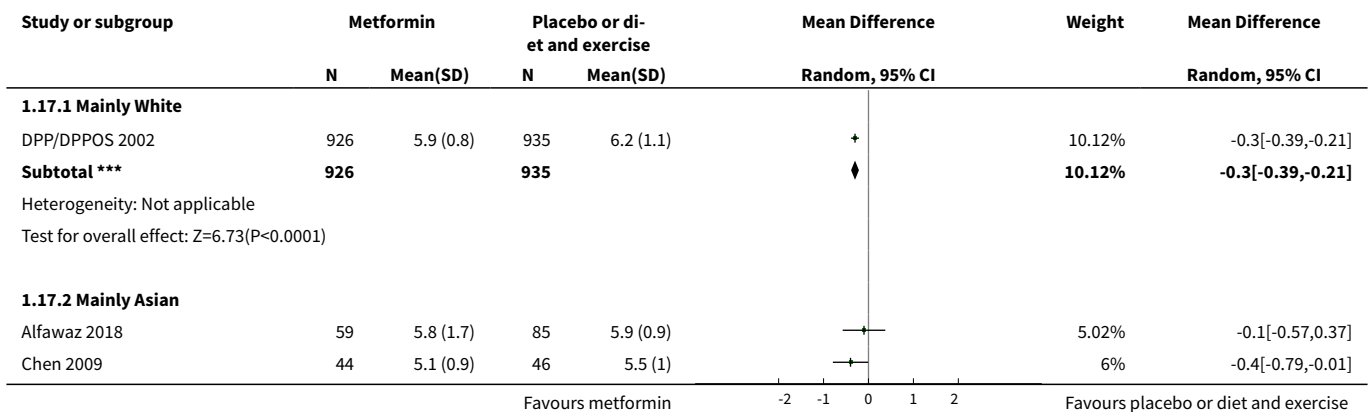
Analysis 1.15. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 15 Fasting plasma glucose (blinded vs open-label).

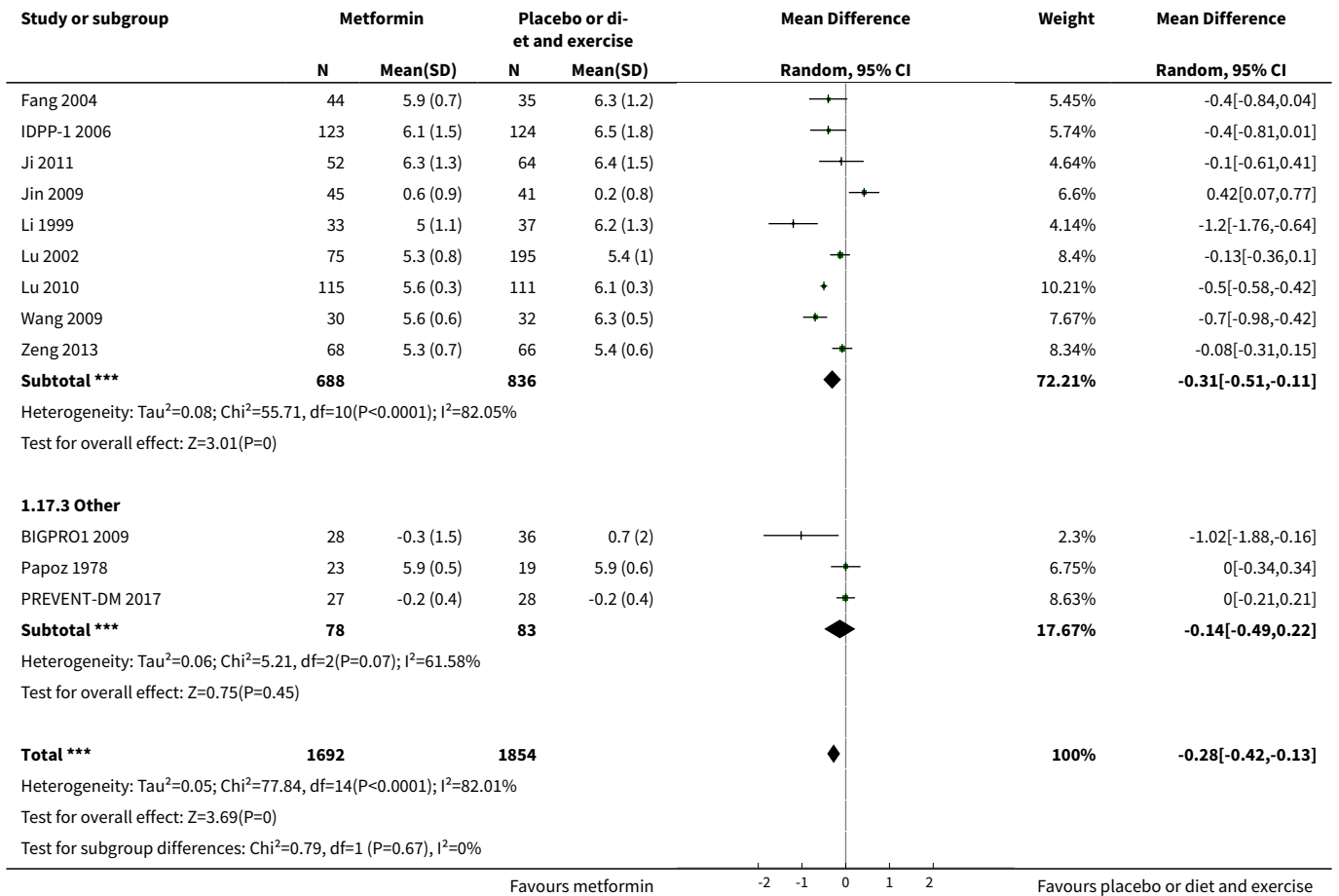


Analysis 1.16. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 16 Fasting plasma glucose (duration of the intervention).



Analysis 1.17. Comparison 1 Metformin versus placebo or diet and exercise, Outcome 17 Fasting plasma glucose (ethnicity).





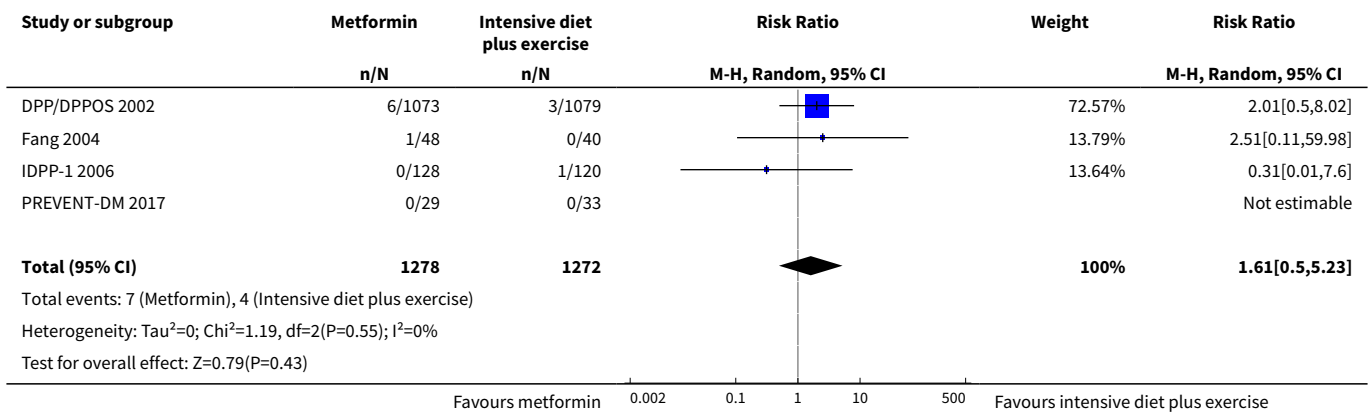
Comparison 2. Metformin versus intensive diet plus exercise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	4	2550	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.50, 5.23]
2 Incidence of type 2 diabetes	7	2960	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.37]
3 Incidence of type 2 diabetes (duration of intervention)	7	2960	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.37]
3.1 Duration of intervention less than 2 years	1	62	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Duration of intervention 2 years or more	6	2898	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.37]
4 Incidence of type 2 diabetes (ethnicity)	7	2960	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.47, 1.37]
4.1 Mainly White	1	2152	Risk Ratio (M-H, Random, 95% CI)	1.51 [1.25, 1.81]

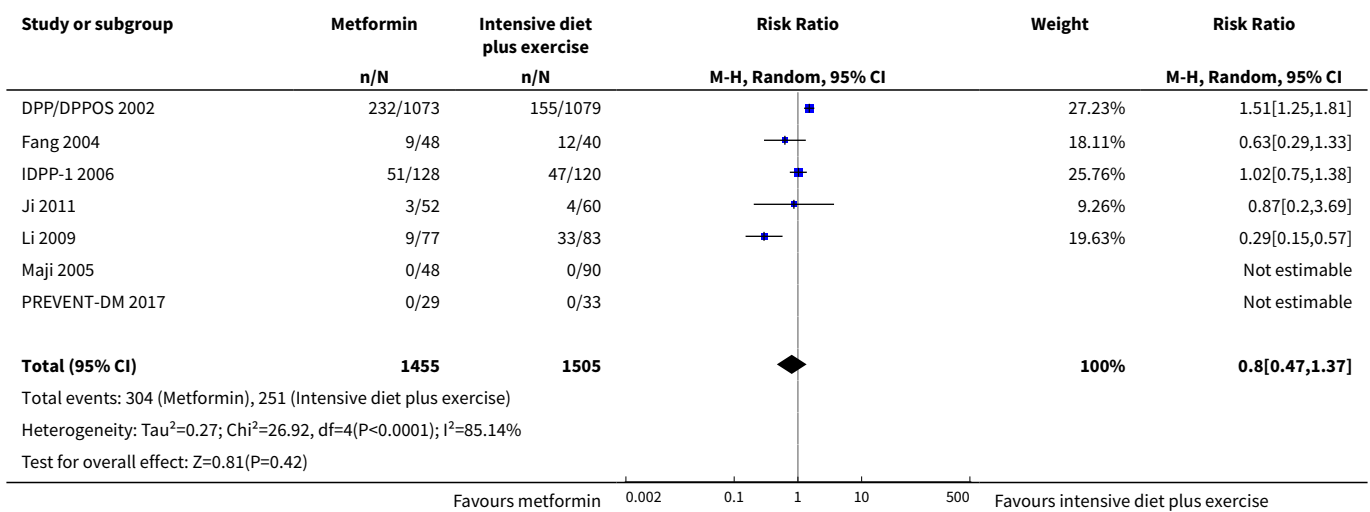
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Mainly Asian	5	746	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.32, 1.24]
4.3 Other	1	62	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 2-hr plasma glucose	5	2417	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.26, 0.20]
6 2-hr plasma glucose (ethnicity)	5	2417	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.26, 0.20]
6.1 Mainly White	1	1834	Mean Difference (IV, Random, 95% CI)	0.20 [0.02, 0.38]
6.2 Mainly Asian	4	583	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.59, 0.17]
6.3 Other	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 HbA1c	4	2135	Mean Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.14]
8 HbA1c (duration of intervention)	4	2135	Mean Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.14]
8.1 Duration of intervention less than 2 years	2	189	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.74, 0.46]
8.2 Duration of intervention 2 years or more	2	1946	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.04, 0.04]
9 HbA1c (ethnicity)	4	2135	Mean Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.14]
9.1 Mainly White	1	1834	Mean Difference (IV, Random, 95% CI)	0.0 [-0.04, 0.04]
9.2 Mainly Asian	2	244	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.66, 0.12]
9.3 Other	1	57	Mean Difference (IV, Random, 95% CI)	0.12 [0.02, 0.22]
10 Fasting plasma glucose	7	2603	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.59, 0.07]
11 Fasting plasma glucose (duration of intervention)	7	2603	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.59, 0.07]
11.1 Duration of intervention less than 2 years	2	189	Mean Difference (IV, Random, 95% CI)	0.02 [-0.17, 0.21]
11.2 Duration of intervention 2 years or more	5	2414	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.79, 0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Fasting plasma glucose (ethnicity)	7	2603	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.59, 0.07]
12.1 Mainly White	1	1831	Mean Difference (IV, Random, 95% CI)	0.0 [-0.07, 0.07]
12.2 Mainly Asian	5	715	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.73, -0.04]
12.3 Other	1	57	Mean Difference (IV, Random, 95% CI)	0.0 [-0.21, 0.21]

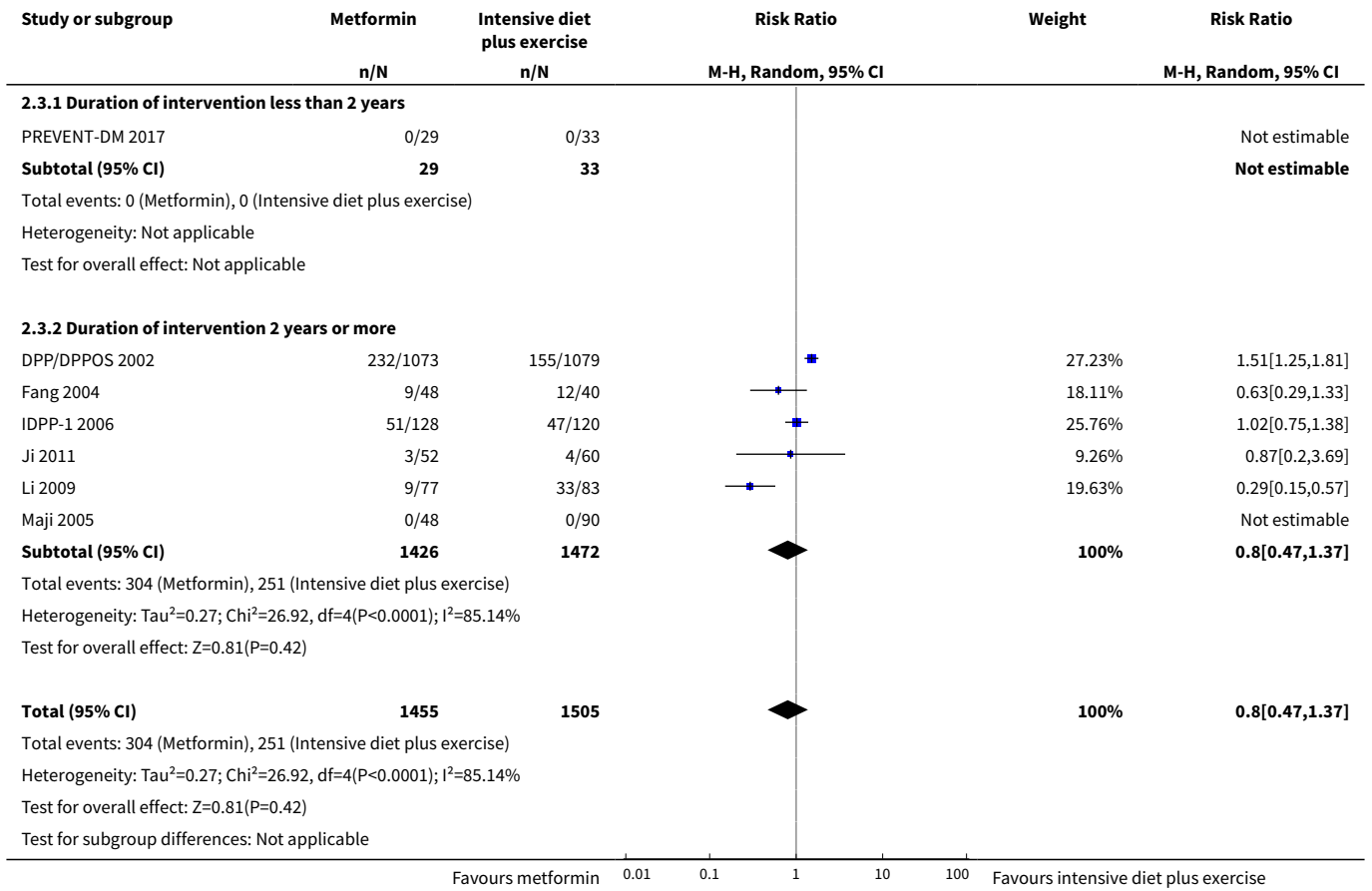
Analysis 2.1. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 1 All-cause mortality.



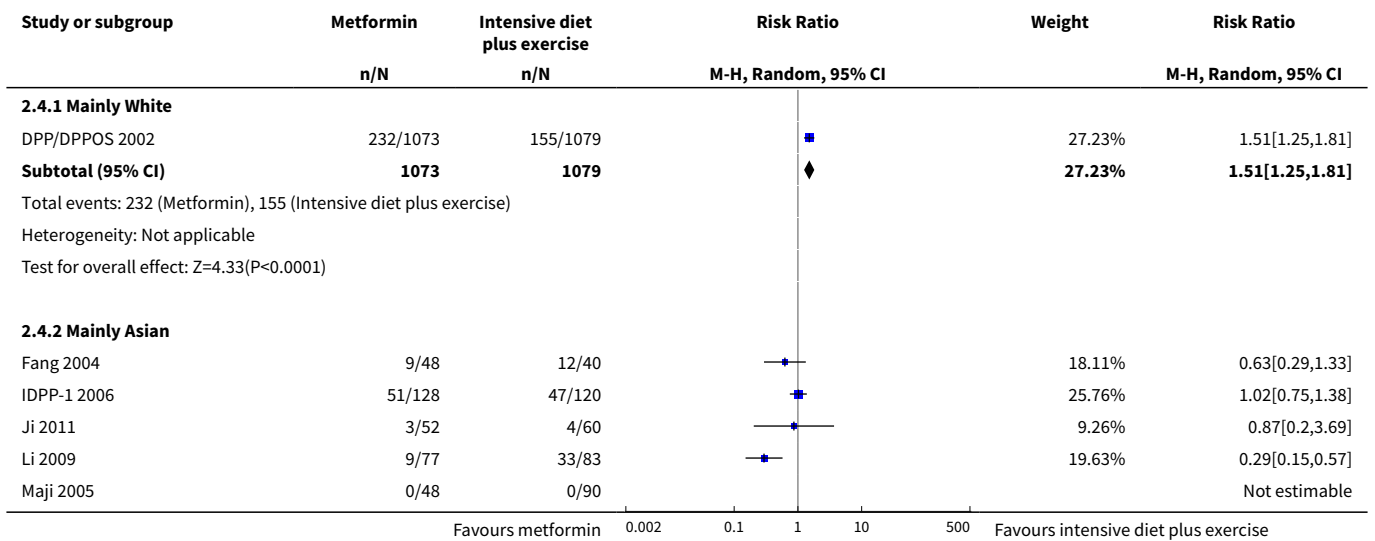
Analysis 2.2. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 2 Incidence of type 2 diabetes.

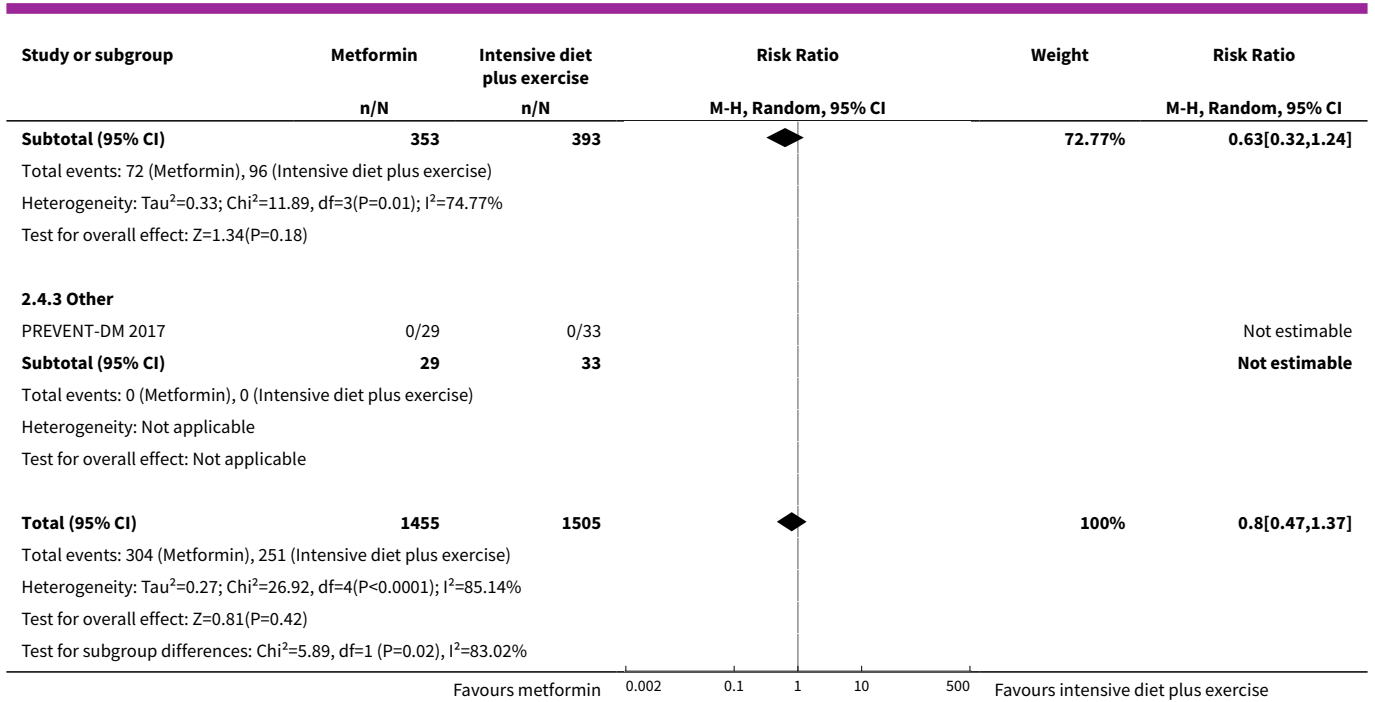


Analysis 2.3. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 3 Incidence of type 2 diabetes (duration of intervention).

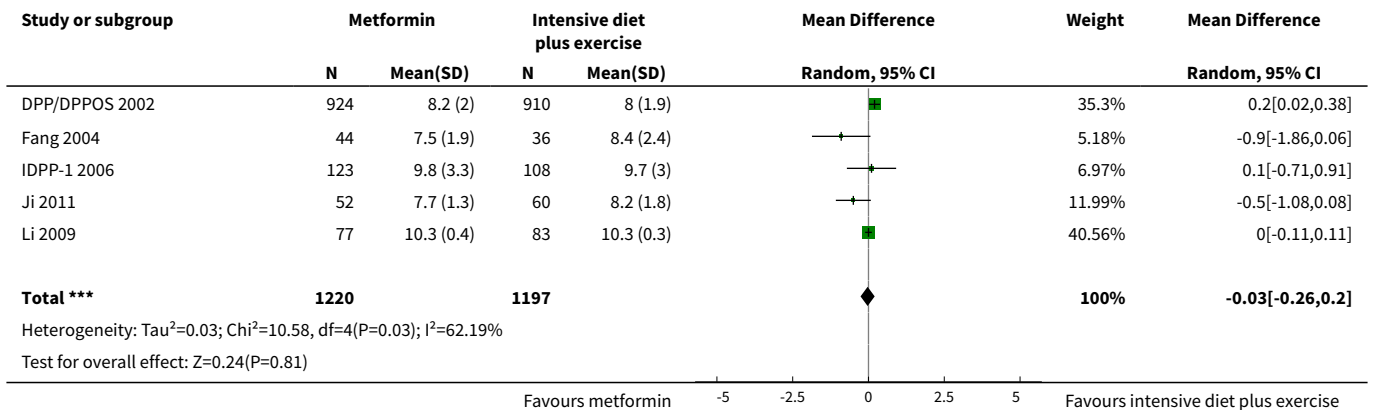


Analysis 2.4. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 4 Incidence of type 2 diabetes (ethnicity).

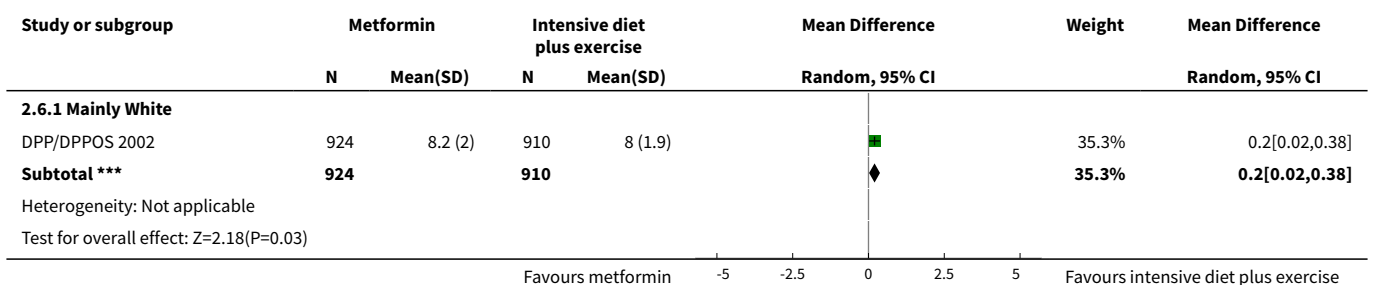


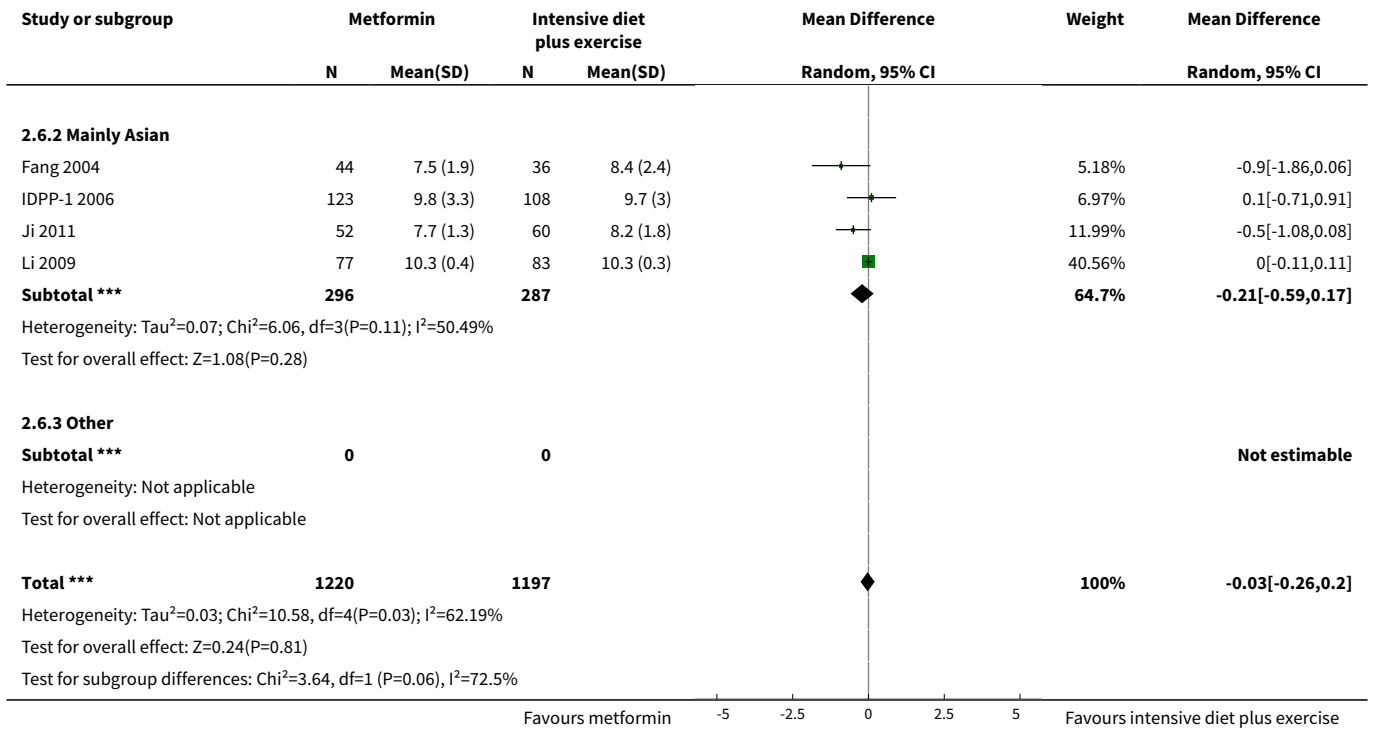


Analysis 2.5. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 5 2-hr plasma glucose.

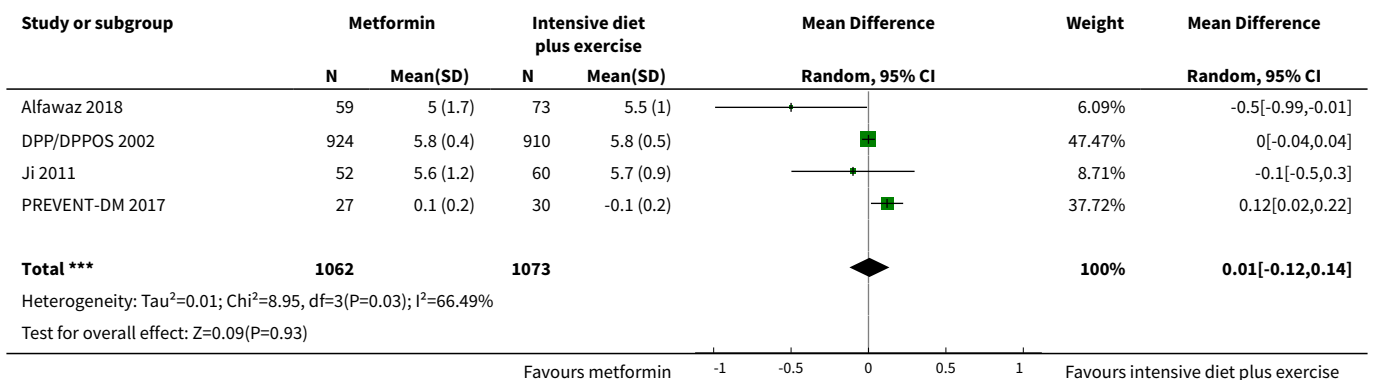


Analysis 2.6. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 6 2-hr plasma glucose (ethnicity).

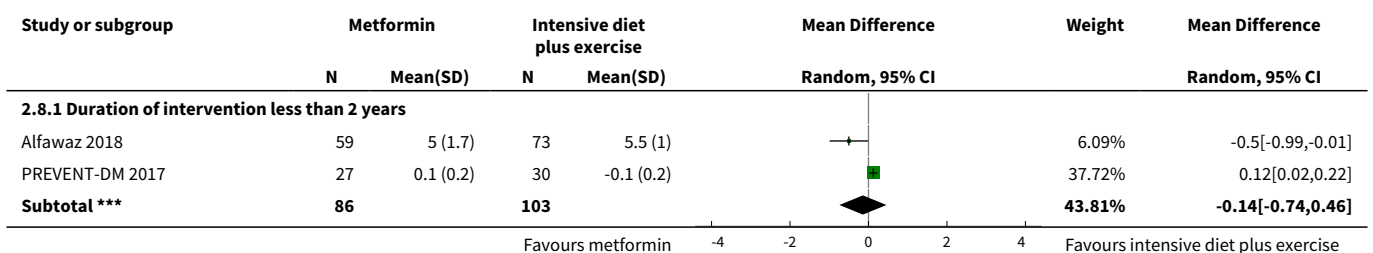


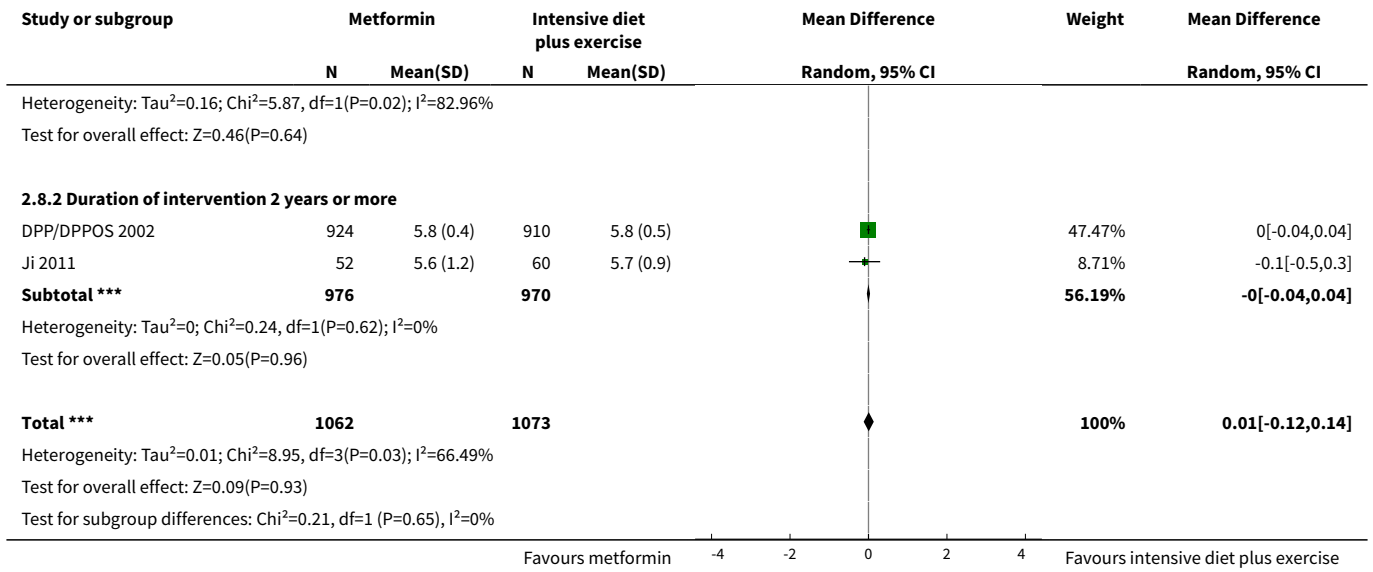


Analysis 2.7. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 7 HbA1c.

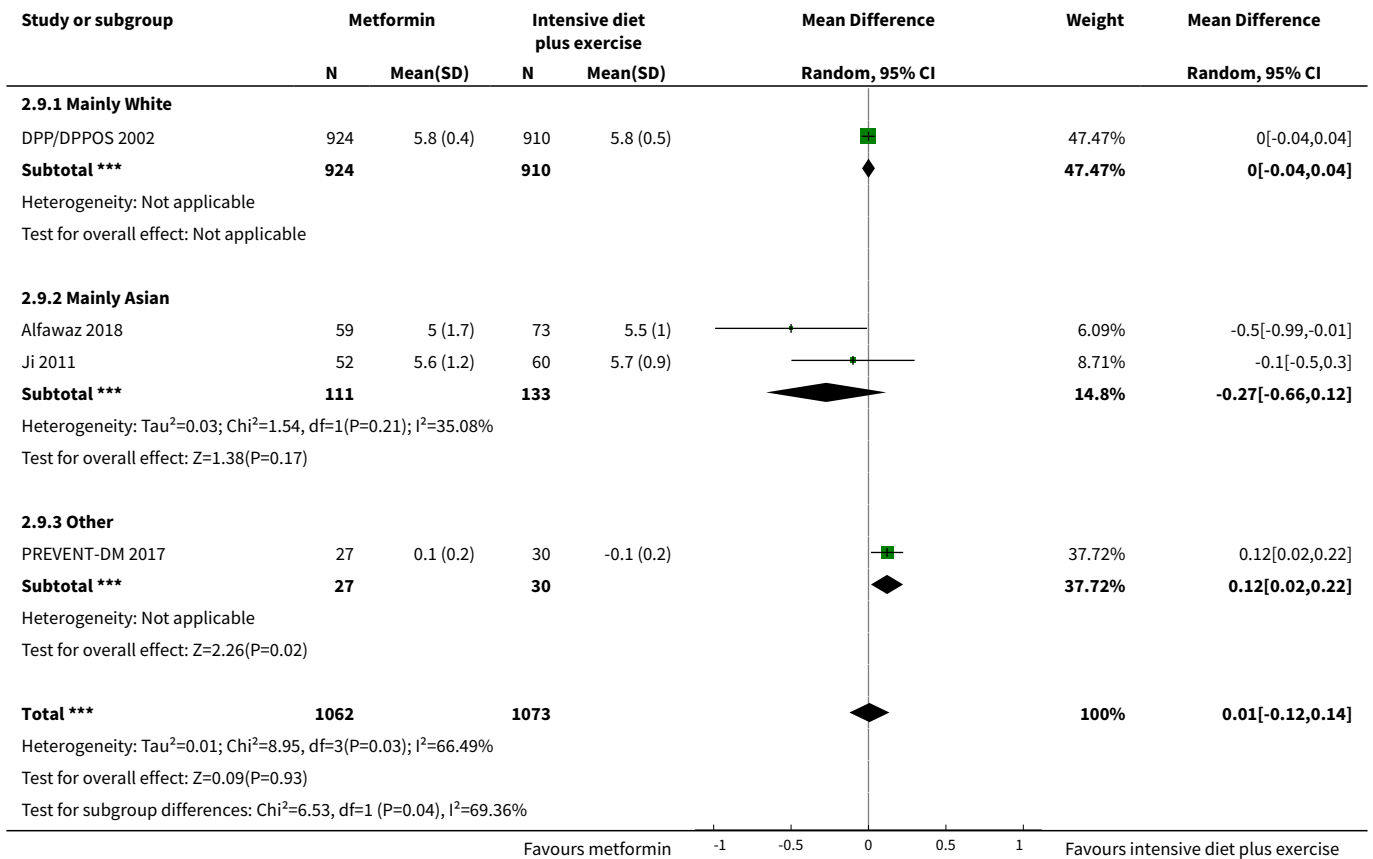


Analysis 2.8. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 8 HbA1c (duration of intervention).

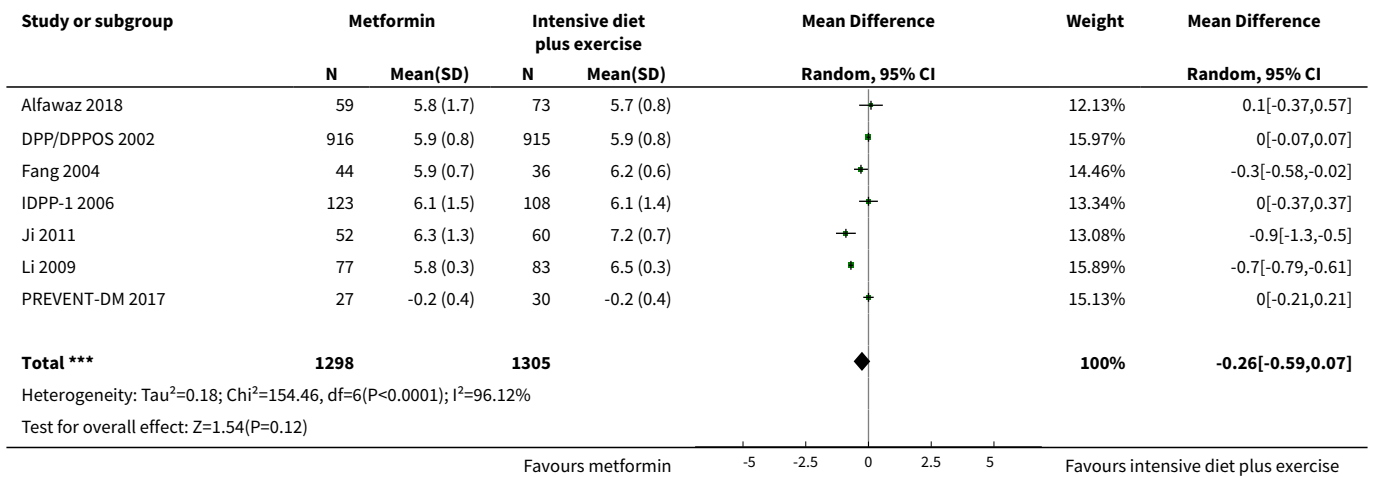




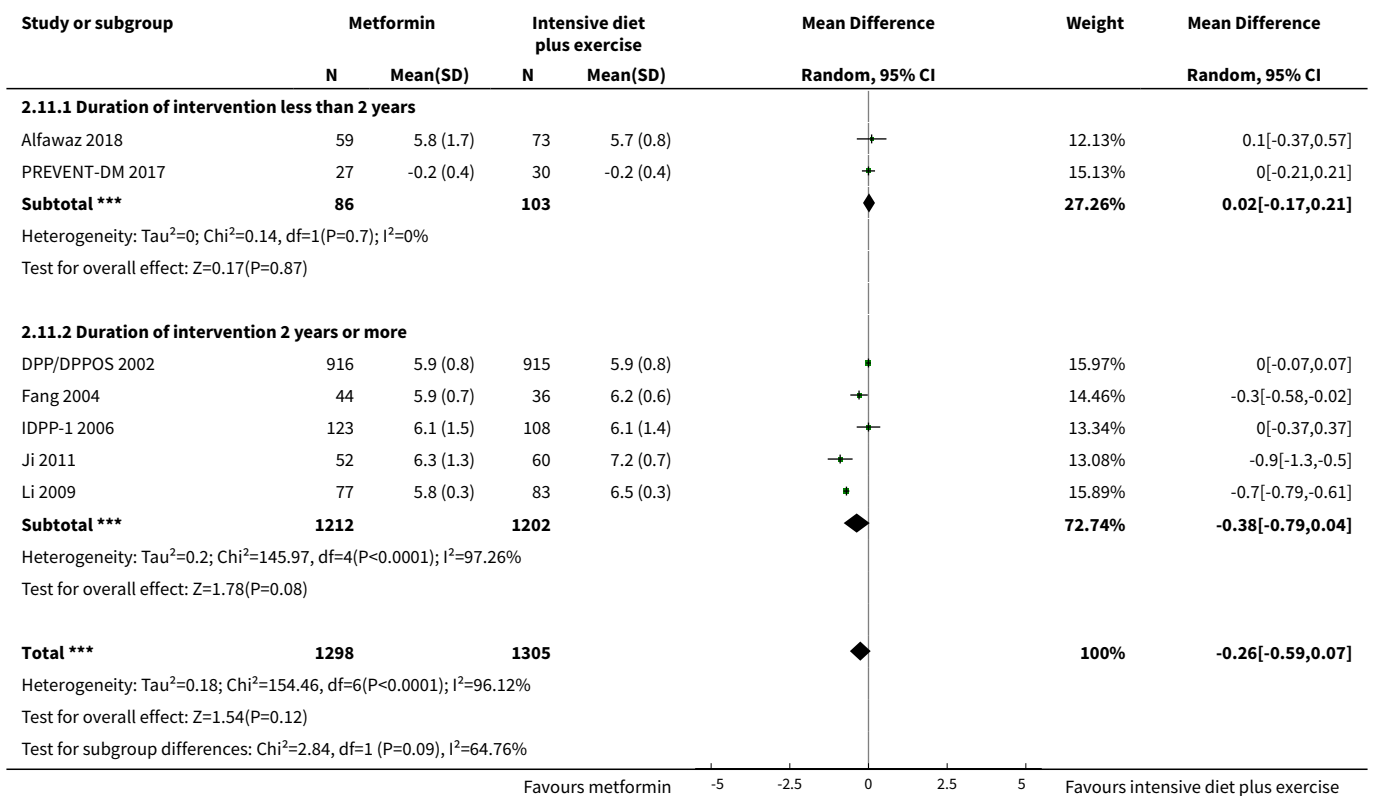
Analysis 2.9. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 9 HbA1c (ethnicity).



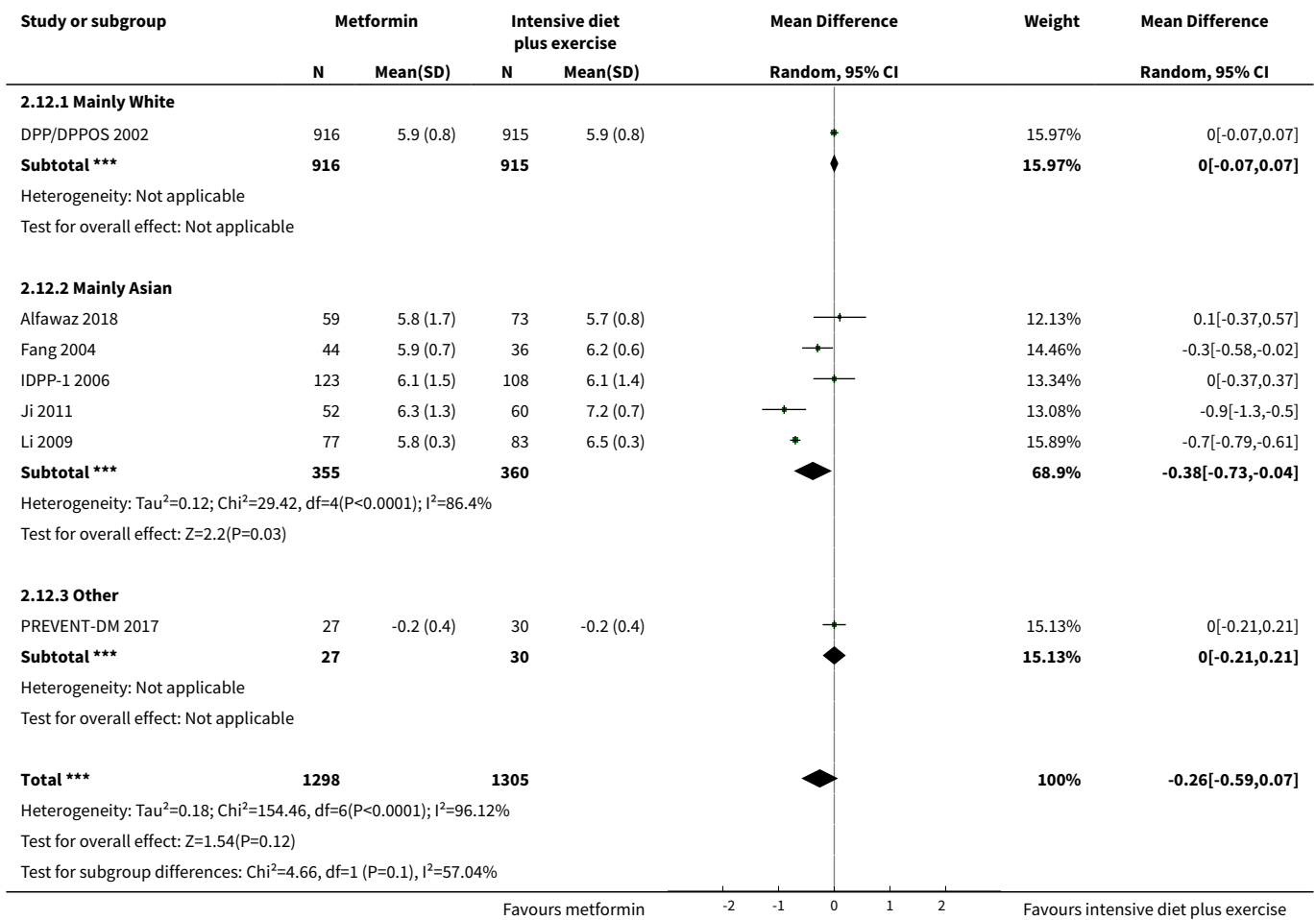
Analysis 2.10. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 10 Fasting plasma glucose.



Analysis 2.11. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 11 Fasting plasma glucose (duration of intervention).



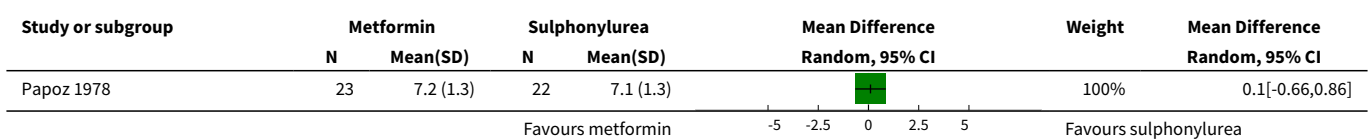
Analysis 2.12. Comparison 2 Metformin versus intensive diet plus exercise, Outcome 12 Fasting plasma glucose (ethnicity).

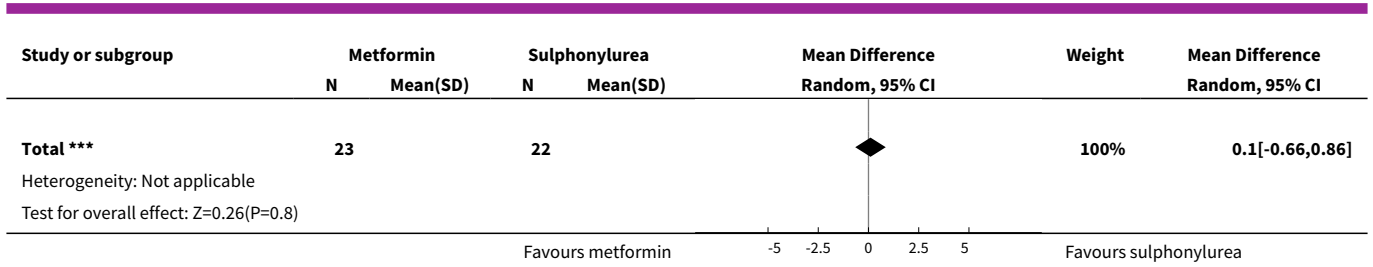


Comparison 3. Metformin versus sulphonylurea

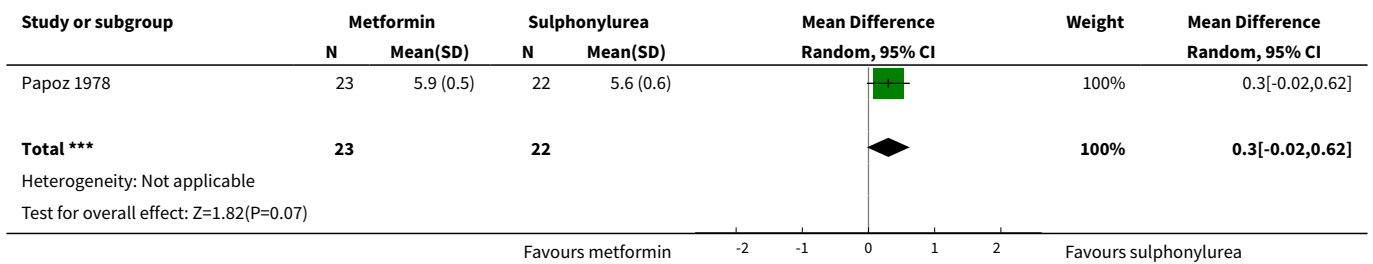
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 2-hr plasma glucose	1	45	Mean Difference (IV, Random, 95% CI)	0.10 [-0.66, 0.86]
2 Fasting plasma glucose	1	45	Mean Difference (IV, Random, 95% CI)	0.30 [-0.02, 0.62]

Analysis 3.1. Comparison 3 Metformin versus sulphonylurea, Outcome 1 2-hr plasma glucose.





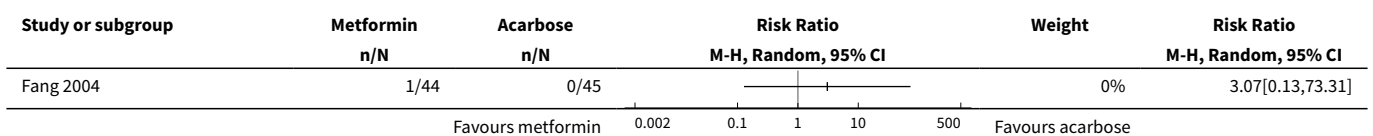
Analysis 3.2. Comparison 3 Metformin versus sulphonylurea, Outcome 2 Fasting plasma glucose.



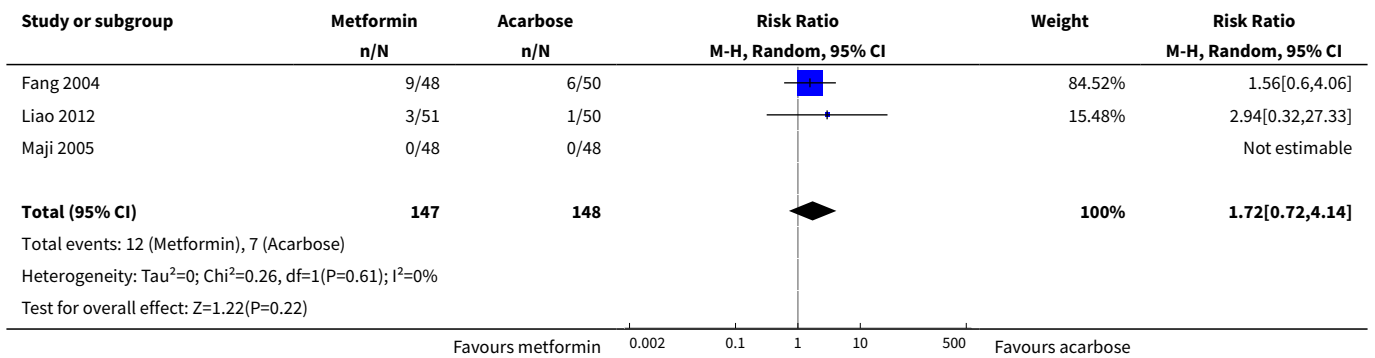
Comparison 4. Metformin versus acarbose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Incidence of type 2 diabetes	3	295	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.72, 4.14]
3 2-hr plasma glucose	2	190	Mean Difference (IV, Random, 95% CI)	0.49 [0.09, 0.88]
4 Fasting plasma glucose	2	190	Mean Difference (IV, Random, 95% CI)	0.00 [-0.35, 0.35]

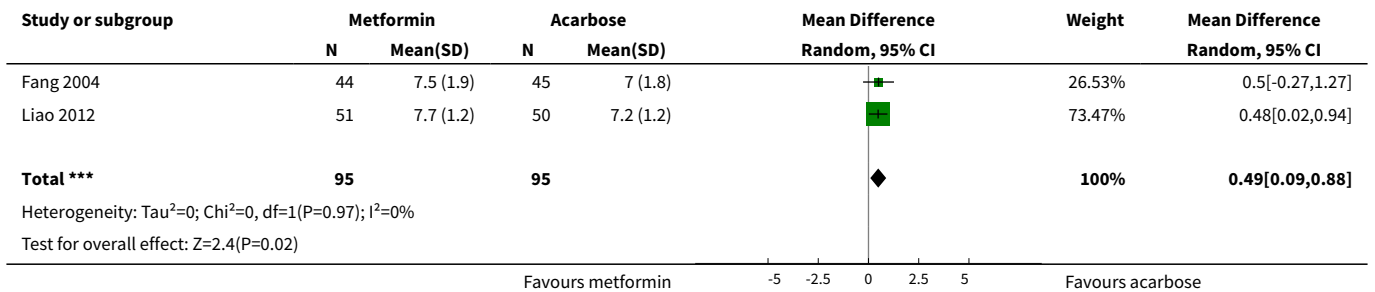
Analysis 4.1. Comparison 4 Metformin versus acarbose, Outcome 1 All-cause mortality.



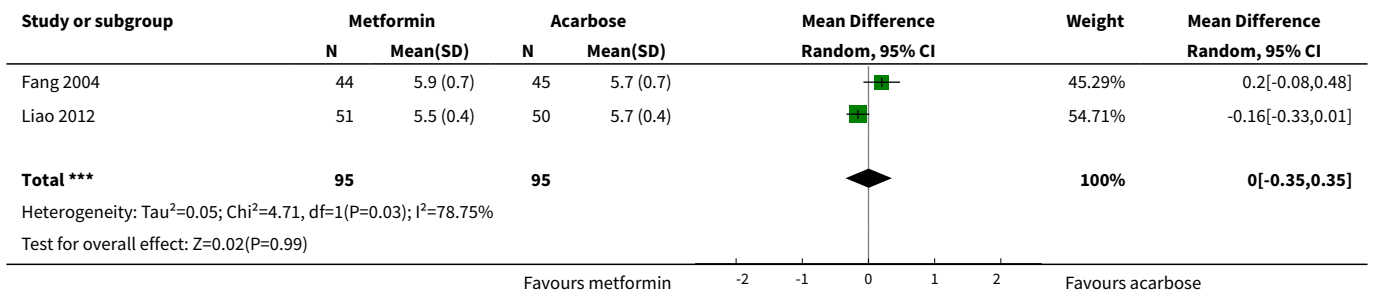
Analysis 4.2. Comparison 4 Metformin versus acarbose, Outcome 2 Incidence of type 2 diabetes.



Analysis 4.3. Comparison 4 Metformin versus acarbose, Outcome 3 2-hr plasma glucose.



Analysis 4.4. Comparison 4 Metformin versus acarbose, Outcome 4 Fasting plasma glucose.

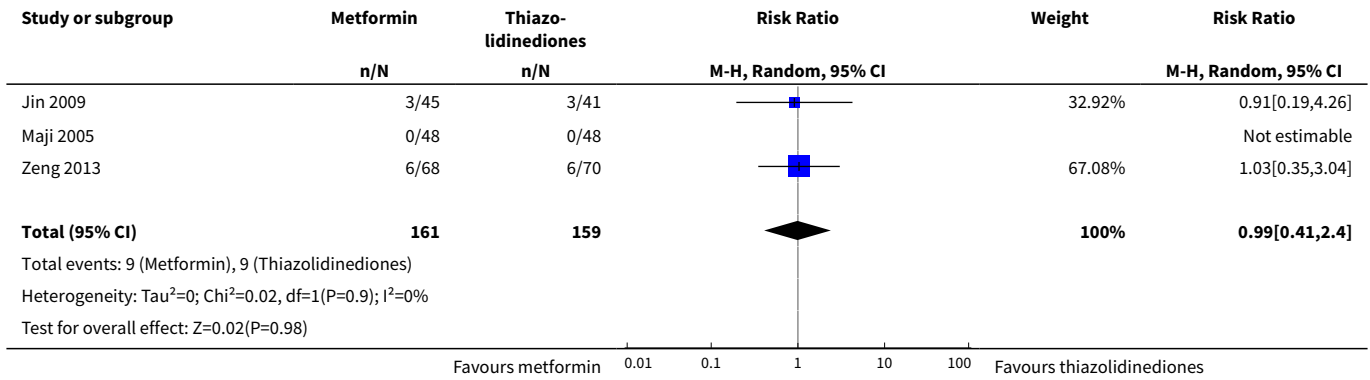


Comparison 5. Metformin versus thiazolidinediones

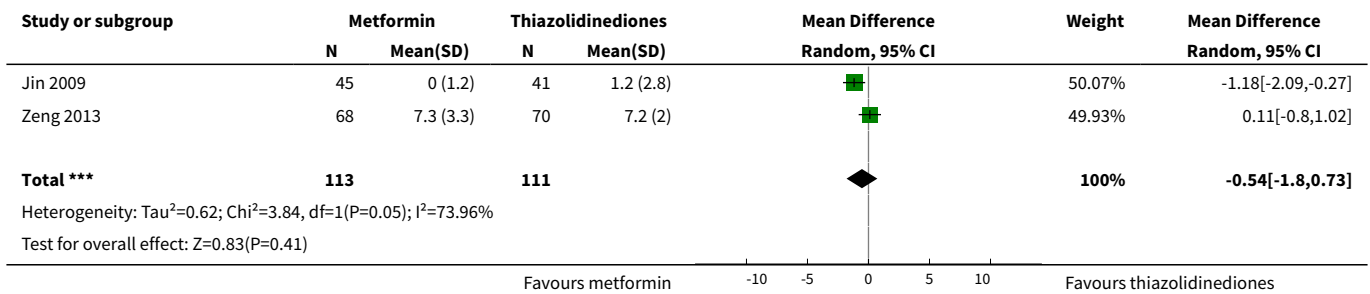
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of type 2 diabetes	3	320	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.41, 2.40]
2 2-hr plasma glucose	2	224	Mean Difference (IV, Random, 95% CI)	-0.54 [-1.80, 0.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Fasting plasma glucose	2	224	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.32, 0.07]

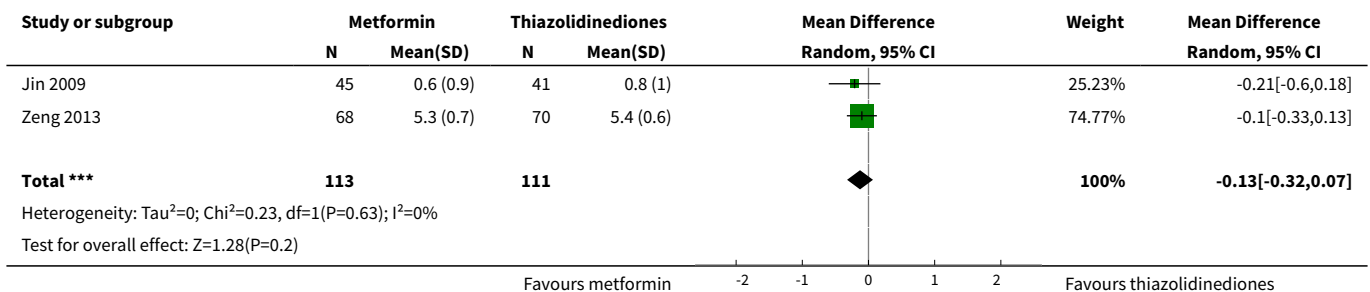
Analysis 5.1. Comparison 5 Metformin versus thiazolidinediones, Outcome 1 Incidence of type 2 diabetes.



Analysis 5.2. Comparison 5 Metformin versus thiazolidinediones, Outcome 2 2-hr plasma glucose.



Analysis 5.3. Comparison 5 Metformin versus thiazolidinediones, Outcome 3 Fasting plasma glucose.



Comparison 6. Metformin + intensive diet and exercise versus intensive diet and exercise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2 Incidence of type 2 diabetes	2	332	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.10, 2.92]
3 Incidence of type 2 diabetes (blinded vs open-label)	3	524	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.58]
3.1 Participants blinded	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Open-label	3	524	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.58]
4 Incidence of type 2 diabetes (duration of the intervention)	3	524	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.58]
4.1 Duration of the intervention less than 2 years	2	283	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.09, 3.42]
4.2 Duration of the intervention 2 years or more	1	241	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.72, 1.36]
5 Incidence of type 2 diabetes (ethnicity)	3	524	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.58]
5.1 mainly White	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 mainly Asian	3	524	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.53, 1.58]
5.3 Other	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 2-hr glucose values	2	316	Mean Difference (IV, Random, 95% CI)	-0.52 [-2.08, 1.04]
7 Fasting plasma glucose	2	316	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.94, 0.43]
8 Fasting plasma glucose (blinded vs open-label)	2	316	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.94, 0.43]
8.1 Participants blinded	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Open-label	2	316	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.94, 0.43]
9 Fasting plasma glucose (duration of the intervention)	2	316	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.94, 0.43]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Duration of the intervention less than 2 years	1	91	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.97, -0.23]
9.2 Duration of the intervention 2 years or more	1	225	Mean Difference (IV, Random, 95% CI)	0.10 [-0.32, 0.52]

Analysis 6.1. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 1 All-cause mortality.

Study or subgroup	Metformin + intensive diet and exercise]	Intensive diet and exercise	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
IDPP-1 2006	1/121	1/120		0%	0.99[0.06,15.67]
Iqbal Hydrie 2012	0/95	0/114			Not estimable

Favours metformin + intensive diet and exercise 0.001 0.1 1 10 1000 Favours intensive diet and exercise

Analysis 6.2. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 2 Incidence of type 2 diabetes.

Study or subgroup	Metformin + intensive diet and exercise]	Intensive diet and exercise	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
IDPP-1 2006	47/121	47/120		66.87%	0.99[0.72,1.36]
Zhao 2013	1/45	6/46		33.13%	0.17[0.02,1.36]
Total (95% CI)	166	166		100%	0.55[0.1,2.92]

Total events: 48 (Metformin + intensive diet and exercise), 53 (Intensive diet and exercise)
Heterogeneity: Tau²=1.05; Chi²=2.83, df=1(P=0.09); I²=64.67%
Test for overall effect: Z=0.7(P=0.49)

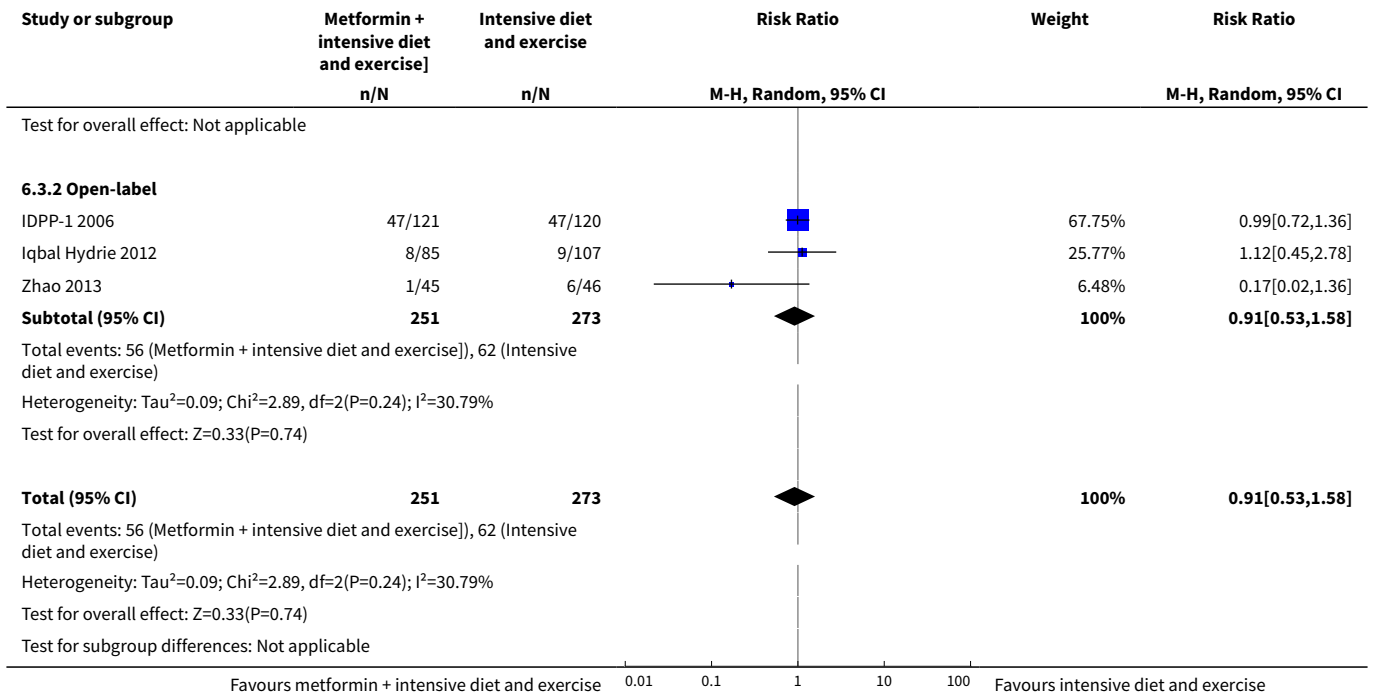
Favours metformin + intensive diet and exercise 0.001 0.1 1 10 1000 Favours intensive diet and exercise

Analysis 6.3. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 3 Incidence of type 2 diabetes (blinded vs open-label).

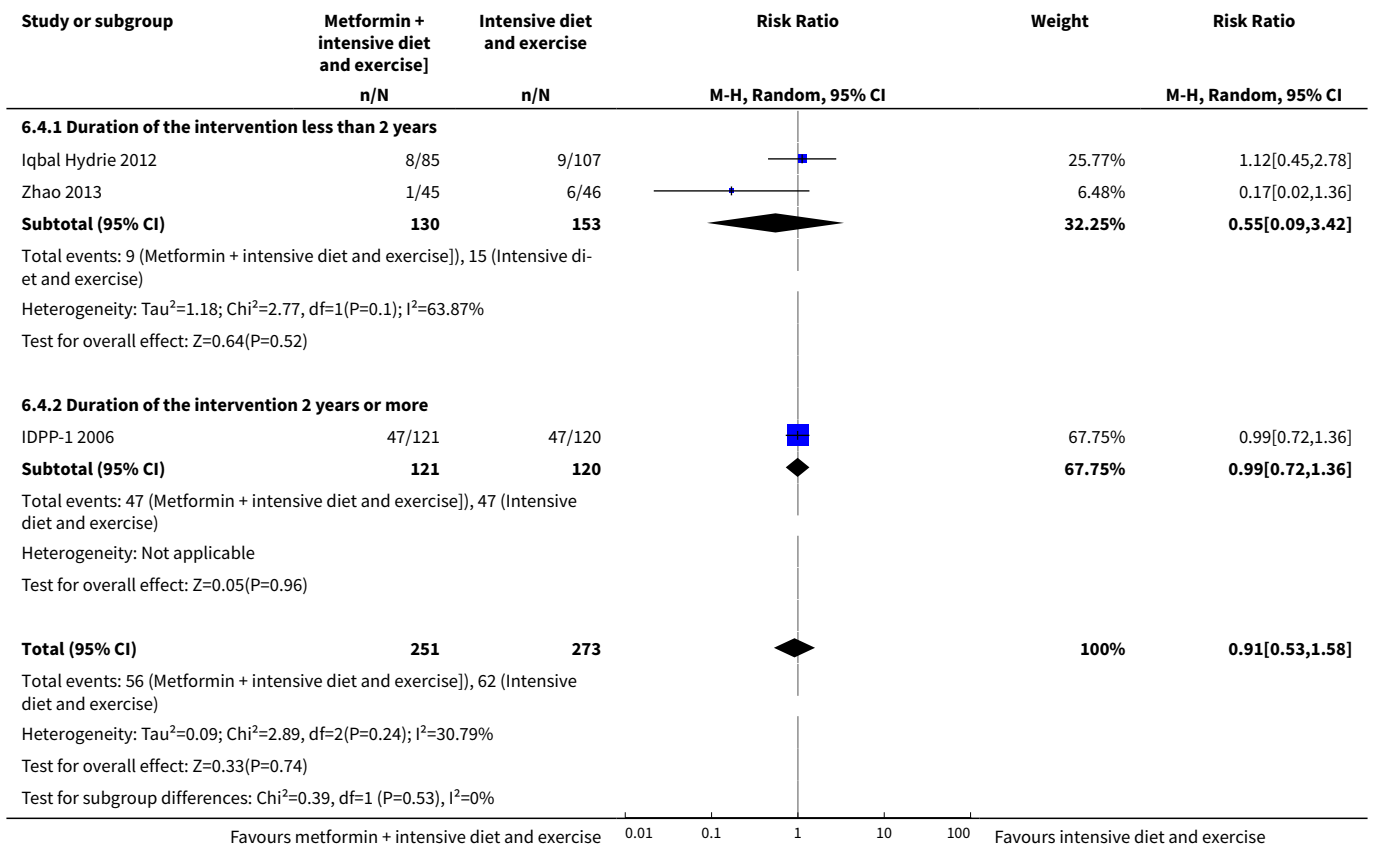
Study or subgroup	Metformin + intensive diet and exercise]	Intensive diet and exercise	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
6.3.1 Participants blinded					
Subtotal (95% CI)	0	0			Not estimable

Total events: 0 (Metformin + intensive diet and exercise), 0 (Intensive diet and exercise)
Heterogeneity: Not applicable

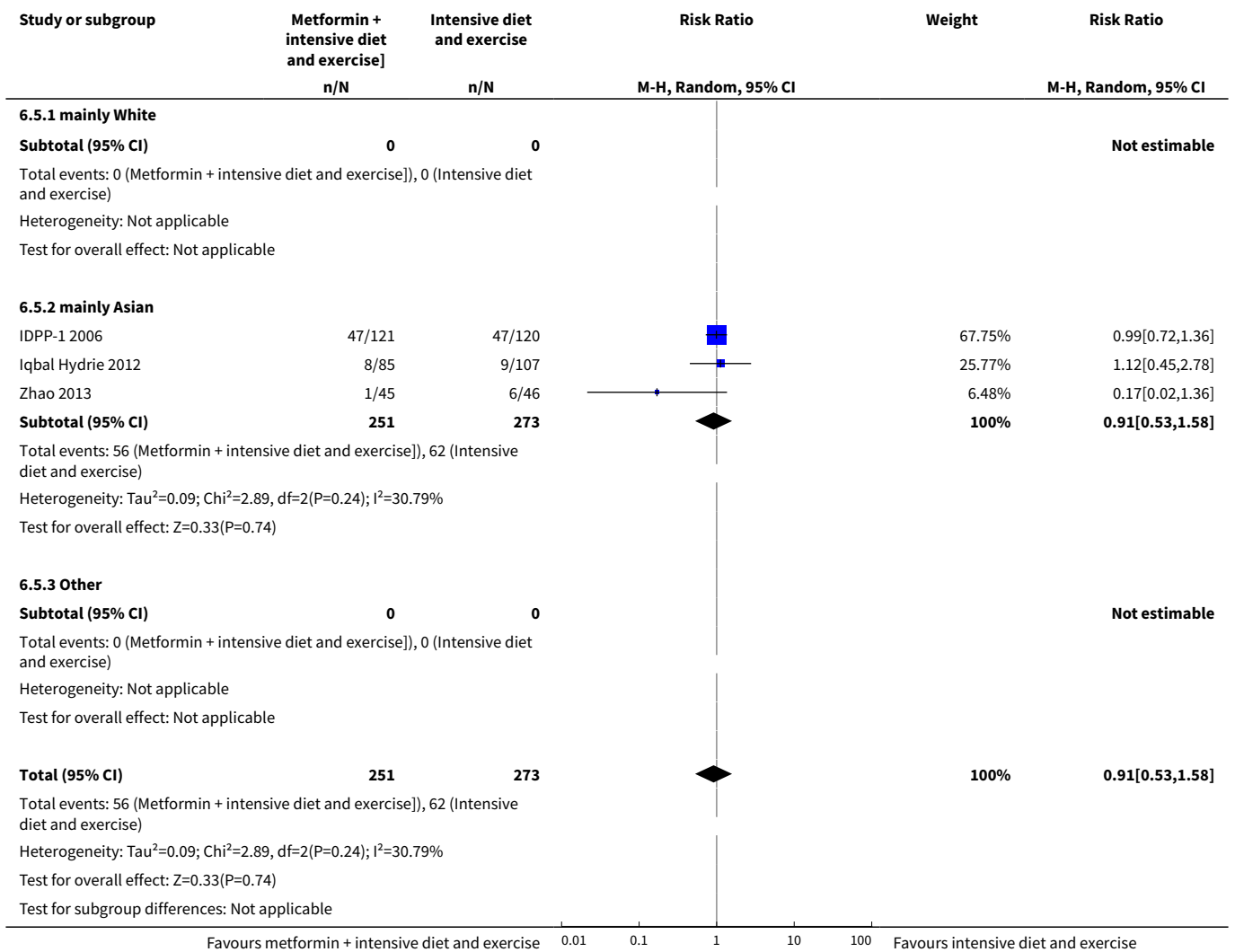
Favours metformin + intensive diet and exercise 0.01 0.1 1 10 100 Favours intensive diet and exercise



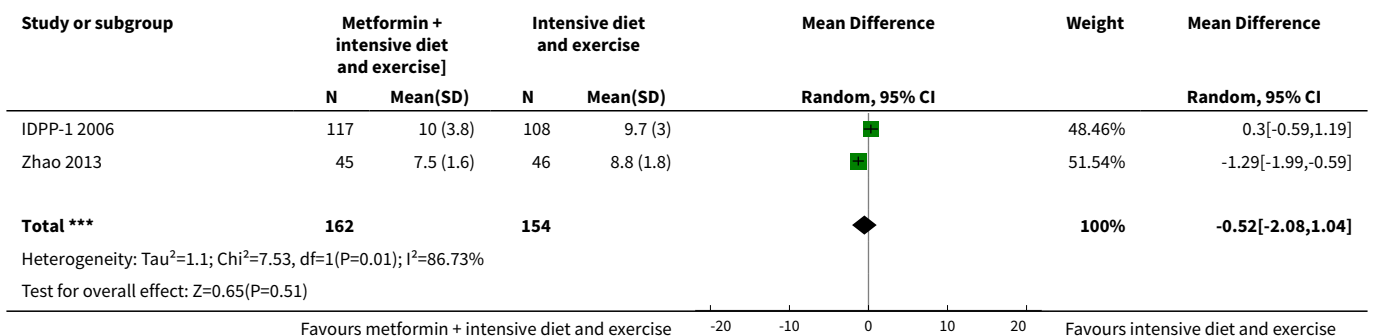
Analysis 6.4. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 4 Incidence of type 2 diabetes (duration of the intervention).



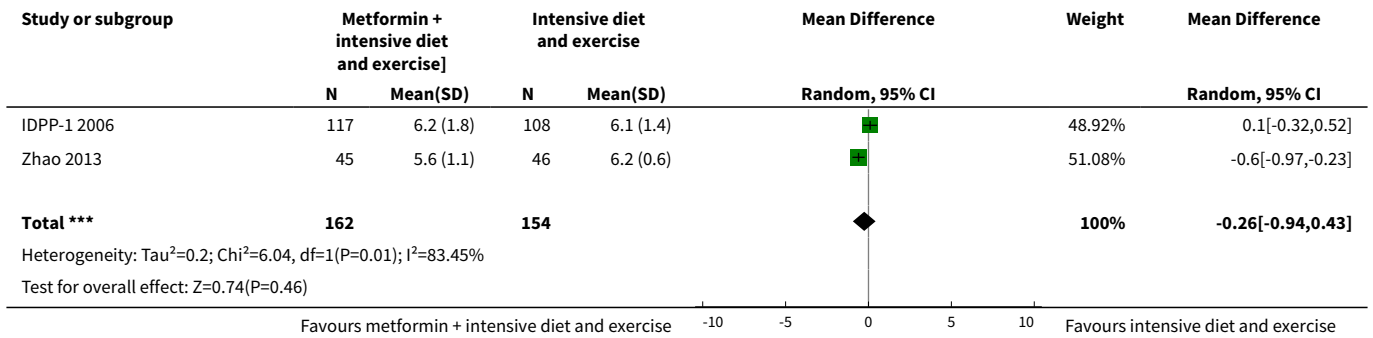
Analysis 6.5. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 5 Incidence of type 2 diabetes (ethnicity).



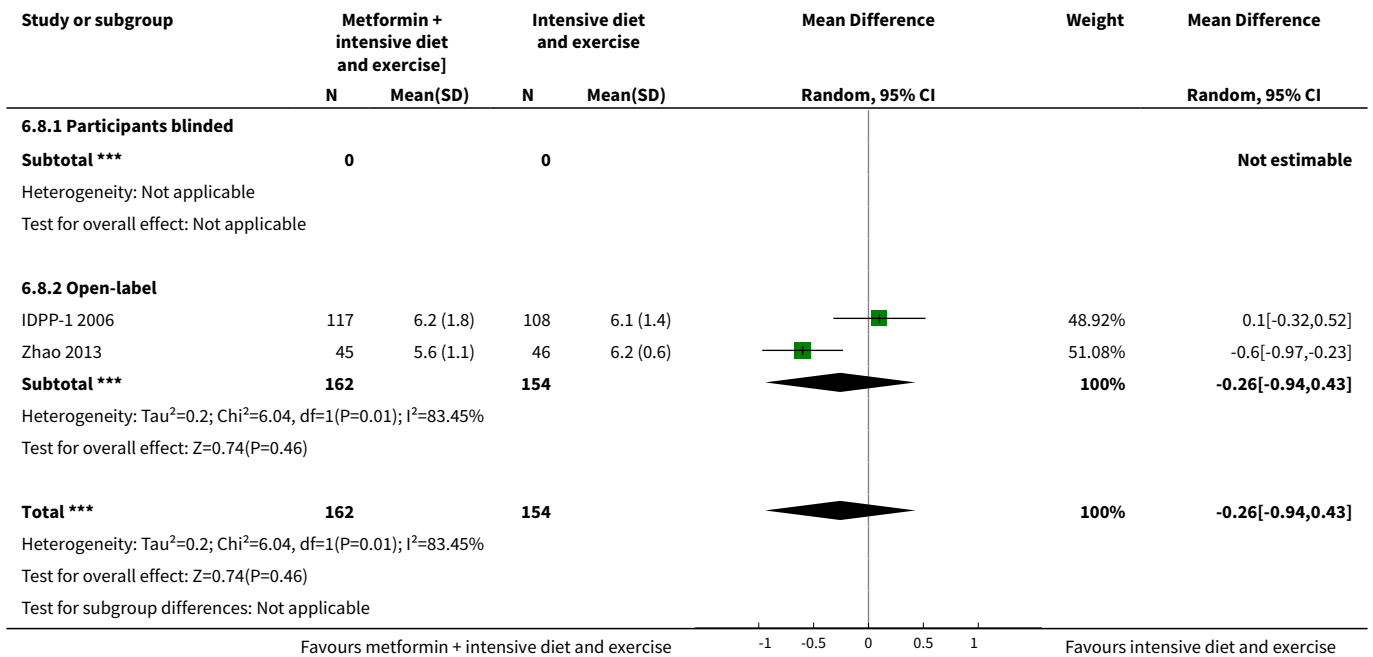
Analysis 6.6. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 6 2-hr glucose values.



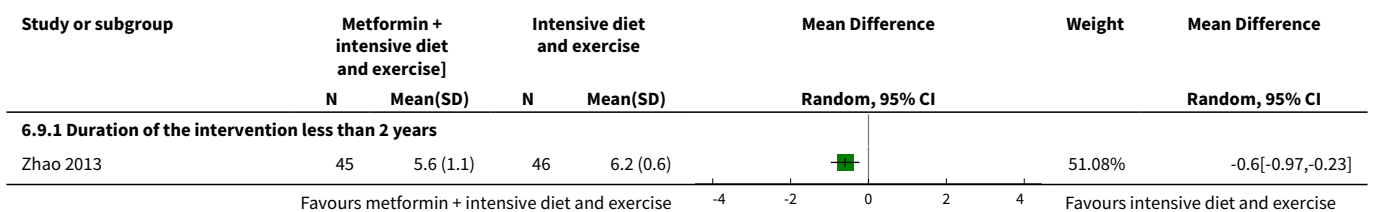
Analysis 6.7. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 7 Fasting plasma glucose.

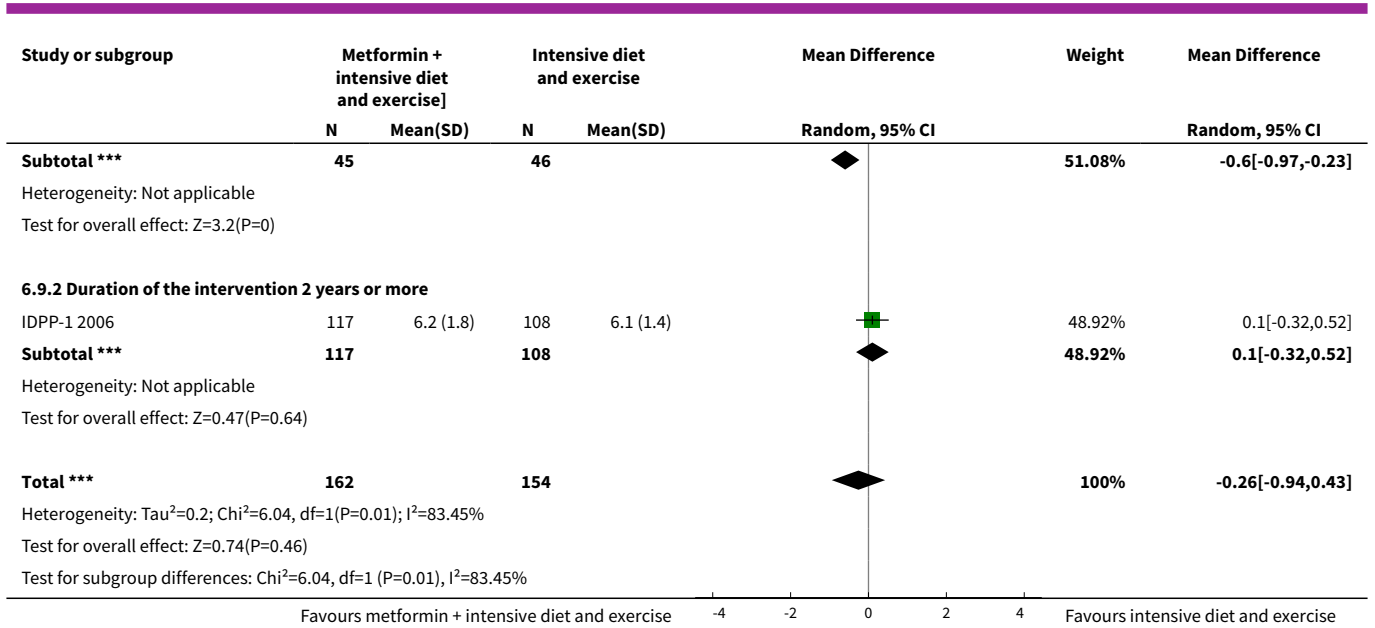


Analysis 6.8. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 8 Fasting plasma glucose (blinded vs open-label).



Analysis 6.9. Comparison 6 Metformin + intensive diet and exercise versus intensive diet and exercise, Outcome 9 Fasting plasma glucose (duration of the intervention).





ADDITIONAL TABLES
Table 1. Overview of trial populations

Trial (de-sign)	Intervention(s) and comparator(s)	Description of power and sample size calculation	Screened/eligible (N)	Ran-domised (N)	Analysed (N)	Finishing trial (N)	Ran-domised finishing trial (%)	Follow-up (extended follow-up) ^a
Alfawaz 2018 (parallel RCT)	I: metformin	—	—	98	59	68	69.4	1 year (1 year)
	C1: intensive diet plus exercise			98	73	75	76.5	
	C2: standard care			98	85	94	95.9	
	total:			294	217	237	80.6	
PRE-VENT-DM 2017 (parallel RCT) NCT02088034	I1: metformin	Quote: "Data from a previous pilot study of the promotora-led ILI provided estimates for participant retention at 12-month follow-up (90%) and 12-month weight loss (4.9 kg, SD 4.9 kg). Based on these assumptions, the enrollment target was 30 participants per study arm in order to retain 27 in each group at 12 months. These assumptions allowed for >80% power to detect a mean weight loss difference of at least 4.9 kg (SD=4.9 kg) between groups, which was lower than that observed in DPP, at the overall 5% significance level. Power calculations adjusted for three pairwise comparisons, using a 1.7% significance level for each"	441/197	29	27	27	93.1	1 year (—)
	C1: intensive diet plus exercise			33	30	30	90.9	
	C2: standard care			30	28	28	93.3	
	total:			92	85	85	92.4	
Zeng 2013 (parallel RCT)	I: metformin	—	—	68	68	68	100	2 years
	C1: Standard care			66	66	66	100	
	C2: pioglitazone			70	70	70	100	
	total:		204	204	204	100		

Table 1. Overview of trial populations (Continued)

Zhao 2013 (parallel RCT)	I: metformin plus intensive diet plus exercise	—	—	46	45	45	97.8	1 year
	C: intensive diet plus exercise			46	46	46	97.8	
	total:			92	91	91	98.9	
Iqbal Hydrie 2012 (parallel RCT)	I1: metformin plus intensive diet and exercise	Quote: "Mean and standard deviation were reported for continuous variables and intergroup comparisons were tested by two tailed ANOVA. Comparison of proportions was by χ^2 analysis. The proportion of subjects developing diabetes in each group and their comparison was by χ^2 analysis. For the intervention measures, the absolute and relative risk reductions, 95% CIs of the estimates, and the number needed to treat to prevent diabetes in one person were calculated. A P value <0.05 was considered significant"	1739/317	95	85	85	89.5	18 months (—)
	C1: intensive diet and exercise			114	107	107	93.9	
	C2: standard care			108	82	82	75.9	
	total:			317	274	274	86.4	
Liao 2012 (parallel RCT)	I: metformin	—	—	52	50	50	96.2	1 year
	C: acarbose			52	51	51	98.1	
	total:			104	101	101	97.1	
Ji 2011 (parallel RCT)	I1: metformin	—	—	52	52	52	100	2 years
	C1: intensive diet plus exercise			60	60	60	100	
	C2: standard care			64	64	64	100	
	total:			176	176	176	100	
Lu 2010	I: metformin	—	—	117	115	96	82	2 years

Table 1. Overview of trial populations (Continued)

(parallel RCT)	C: standard care			117	111	100	85.5	
	total:			234	226	196	83.8	
BIGPRO1 2009 ^b (parallel RCT)	S1 - I1: metformin	Quote: "Given the number of variable to be compared, the required sample size fluctuate between 200 and 500 per group, according to the variable under consideration and allowing for multiple testing (two-tailed test, $\alpha = \beta = 5\%$)."	S1: 457/101 S2: 457/51	49	28	28	57.1	1 year (—)
	S1 - C1: placebo		52	36	36	69.2		
	S2 - I1: metformin		28	18	18	64.3		
	S2 - C1: placebo		23	14	14	60.9		
	total S1:		101	64	64			
total S2:	51	32	32					
Chen 2009 (parallel RCT)	I: metformin	—	—	49	44	44	89.8	2 years
	C: standard care			52	46	46	88.5	
	total:			101	90	90	89.1	
Jin 2009 (parallel RCT)	I: metformin	—	—	48	45	45	93.8	3 years
	C1: standard care			41	41	41	100	
	C2: rosiglitazone			44	41	41	93.2	
	total:			133	127	127	95.5	
Li 2009 (parallel RCT)	I: metformin	—	—	77	77	74	96.1	3 years
	C: intensive diet plus exercise			83	83	79	95.2	
	total:			160	160	153	95.6	
Wang 2009 (parallel RCT)	I: metformin	—	—	32	30	30	93.8	1 year
	C: standard care			32	32	32	100	
	total:			64	62	62	96.9	

Table 1. Overview of trial populations (Continued)

IDPP-1 2006 (parallel RCT)	I1: metformin	Quote: "It was assumed that the cumulative incidence of diabetes in 3 years would be approximately 30% in the control group and that there would be a 50% reduction with the intervention methods. The sample size required in each of the four subgroups was 134 with a type 1 error of 5%, 80% power, and allowing for a dropout rate of 10%"	10,839/531	133	128	128	96.2	3 years (—)
	I2: metformin plus intensive diet and physical activity			129	121	121	93.8	
	C1: intensive exercise plus diet			133	120	120	90.2	
	C2: standard care			136	133	133	97.8	
total:				531	502	502	94.5	
Maji 2005 (parallel RCT)	I1: metformin	—	234/234	48	—	—	—	3 years (—)
	C1: intensive lifestyle intervention			90	—	—	—	
	C2: rosiglitazone			48	—	—	—	
	C3: acarbose			48	—	—	—	
total:				234	—	—	—	
Fang 2004 (parallel RCT)	I: metformin	—	1549/178	48	44	44	91.7	5 years (—)
	C1: acarbose			50	45	45	90.0	
	C2: intensive exercise and diet			40	36	36	90.0	
	C3: standard care			40	35	35	87.5	
total:				178	160	160	89.9	
DPP/DPPOS 2002 (parallel RCT)	I: metformin	Quote: "The principal analyses of primary and secondary outcomes will employ the "intent-to-treat" approach (Peduzzi, Wittes, et al., 1993). The intent-to-treat analyses will include all randomized participants with all participants included in their randomly assigned treatment group;	153,183	1073	—	—	—	2.8 years (15 years)
	C1: intensive exercise and diet			1079	—	—	—	
	C2: placebo			1082	—	—	—	

Table 1. Overview of trial populations (Continued)

treatment group assignment will not be altered based on the participant's adherence to the assigned treatment regimen. All statistical tests will be two-sided. The overall significance level of the primary outcome will be $\alpha = 0.05$. However, because interim analyses will be conducted throughout the DPP, the significance levels used in the interim and final analyses of the primary outcome will be adjusted to account for the multiplicity of interim analyses." and "The study design provided 90 percent power to detect a 33 percent reduction from an incidence of 6.5 cases of diabetes per 100 person-years, with a 10 percent rate of loss to follow-up per year"

	total:			3234	3234	—	—	
Lu 2002 (parallel RCT)	I1: metformin	—	—	80	75	75	93.8	3 years
	C1: standard care			72	64	64	88.9	
	C2: standard care plus diet instruction every 6th month			57	51	51	89.5	
	C3: standard care plus fibre diet			84	80	80	95.2	
	total:			293	270	270	92.2	
Li 1999 (parallel RCT)	I1: metformin	—	29,938	45	33	33	73.3	1 year (—)
	C1: placebo			45	37	37	82.2	
	total:			90	70	70	77.8	
Papoz 1978 (parallel RCT)	I1: metformin (plus placebo)	—	—	30	23	23	76.7	2 years (2 years)

Table 1. Overview of trial populations (Continued)

	C1: glibenclamide plus placebo	28	22	22	78.6
	C2: placebo	33	19	19	57.6
	total:	91	64	64	71
Grand total	All interventions	2426			
	All comparators	4348			
	All interventions and comparators	6774			

—: denotes not reported

^aFollow-up under randomised conditions until end of trial or if not available, duration of intervention; extended follow-up refers to follow-up of participants once the original trial was terminated as specified in the power calculation

^bFor BIGPRO1 we evaluated two subgroups available as secondary analyses (published in 2009) from the original trial (1996), which did not meet our inclusion criteria for the population

C: comparator; **I:** intervention; **ITT:** intention-to-treat; **RCT:** randomised clinical trial.

APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Register of Studies Online)

1. MESH DESCRIPTOR Prediabetic state
2. MESH DESCRIPTOR Glucose Intolerance
3. (prediabet* or pre diabet*):TI,AB,KY
4. (intermediate hyperglyc?emi*):TI,AB,KY
5. ((impaired fasting ADJ2 glucose) or IFG or impaired FPG):TI,AB,KY
6. glucose intolerance:TI,AB,KY
7. ((impaired glucose ADJ (tolerance or metabolism)) or IGT):TI,AB,KY
8. ((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) ADJ4 (diabetes or T2D* or NIDDM or "type 2" or "type II")):TI,AB,KY
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. MESH DESCRIPTOR Metformin
11. metformin*:TI,AB,KY
12. #10 OR #11
13. #9 AND #12

MEDLINE (Ovid SP)

1. Prediabetic state/
2. Glucose Intolerance/
3. (prediabet* or pre diabet*).tw.
4. intermediate hyperglyc?emi*.tw.
5. ((impaired fasting adj2 glucose) or IFG or impaired FPG).tw.
6. glucose intolerance.tw.
7. ((impaired glucose adj (tolerance or metabolism)) or IGT).tw.
8. ((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) adj4 (diabetes or T2D* or NIDDM or "type 2" or "type II")).tw.
9. or/1-8
10. Metformin/
11. metformin*.tw.
12. 10 or 11
13. 9 and 12

[14-24: Cochrane Handbook 2008 RCT filter - sensitivity maximizing version]

(Continued)

14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomi?ed.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. or/14-21
23. exp animals/ not humans/
24. 22 not 23
25. 13 and 24
26. ..dedup 25

Scopus

1. KEY("prediabetic state" OR "glucose intolerance" OR "impaired glucose tolerance")
2. TITLE-ABS(prediabet* OR "pre diabet*" OR "intermediate hyperglyc?emi*")
3. TITLE-ABS(("impaired fasting" PRE/3 glucose) OR IFG OR "impaired FPG")
4. TITLE-ABS("glucose intolerance")
5. TITLE-ABS(("impaired glucose" PRE/0 (tolerance OR metabolism)) OR IGT)
6. TITLE-ABS((risk or progress* or prevent* or inciden* or conversion or develop* or delay*) W/4 (diabetes or T2D* or NIDDM or "type 2" or "type II"))
7. #1 OR #2 OR #3 OR #4 OR #5 OR #6
8. TITLE-ABS-KEY(Metformin)
9. #7 AND #8
10. TITLE-ABS-KEY(random* OR "clinical trial*" OR "double blind*" OR placebo*)
11. #9 AND #10
12. #11 AND (LIMIT-TO (DOCTYPE, "ar") OR LIMIT-TO (DOCTYPE, "ip")) [ar = article, ip = article in press]

ICTRP Search Portal (Standard search)

prediabet* AND metformin OR
pre diabet* AND metformin OR
impaired AND glucose* AND metformin OR
impaired AND fasting* AND metformin OR
glucose AND intoleran* AND metformin OR
IFG AND metformin OR
IGT AND metformin

ClinicalTrials.gov (Expert search)

(Continued)

(prediabetes OR prediabetic OR "pre diabetes" OR "pre diabetic" OR "impaired glucose" OR "impaired fasting" OR "glucose intolerance" OR IGT OR IFG OR ((diabetes OR "type 2" OR "type II" OR T2D OR T2DM) AND (risk OR progress OR progression OR progressed OR incident OR incidence OR conversion OR developed OR development OR develop OR delay OR delayed OR prevention OR prevent OR prevented))) [DISEASE] AND metformin [TREATMENT]

Appendix 2. Assessment of risk of bias

Risk of bias domains

Random sequence generation (selection bias due to inadequate generation of a randomised sequence)

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

- Low risk of bias: the study authors achieved sequence generation using computer-generated random numbers or a random numbers table. Drawing of lots, tossing a coin, shuffling cards or envelopes, and throwing dice are adequate if an independent person performed this who was not otherwise involved in the study. We considered the use of the minimisation technique as equivalent to being random.
- Unclear risk of bias: insufficient information about the sequence generation process.
- High risk of bias: the sequence generation method was non-random or quasi-random (e.g. sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number; allocation by judgment of the clinician; allocation by preference of the participant; allocation based on the results of a laboratory test or a series of tests; or allocation by availability of the intervention).

Allocation concealment (selection bias due to inadequate concealment of allocation prior to assignment)

We described for each included study the method used to conceal allocation to interventions prior to assignment and we assessed whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.

- Low risk of bias: central allocation (including telephone, interactive voice-recorder, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
- Unclear risk of bias: insufficient information about the allocation concealment.
- High risk of bias: used an open random allocation schedule (e.g. a list of random numbers); assignment envelopes used without appropriate safeguards; alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

We also evaluated study baseline data to incorporate assessment of baseline imbalance into the 'Risk of bias' judgment for selection bias (Corbett 2014). Chance imbalances may also affect judgments on the risk of attrition bias. In the case of unadjusted analyses, we distinguished between studies that we rated as being at low risk of bias on the basis of both randomisation methods and baseline similarity, and studies that we judged as being at low risk of bias on the basis of baseline similarity alone (Corbett 2014). We reclassified judgements of unclear, low or high risk of selection bias as specified in Appendix 3.

Blinding of participants and study personnel (performance bias due to knowledge of the allocated interventions by participants and personnel during the study)

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of participants and key study personnel was ensured, and it was unlikely that the blinding could have been broken; no blinding or incomplete blinding, but we judge that the outcome is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of participants and study personnel; the study does not address this outcome.
- High risk of bias: no blinding or incomplete blinding, and the outcome is likely to have been influenced by lack of blinding; blinding of study participants and key personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment (detection bias due to knowledge of the allocated interventions by outcome assessment)

(Continued)

We evaluated the risk of detection bias separately for each outcome (Hróbjartsson 2013). We noted whether endpoints were self-reported, investigator-assessed or adjudicated outcome measures (see below).

- Low risk of bias: blinding of outcome assessment is ensured, and it is unlikely that the blinding could have been broken; no blinding of outcome assessment, but we judge that the outcome measurement is unlikely to have been influenced by lack of blinding.
- Unclear risk of bias: insufficient information about the blinding of outcome assessors; the study did not address this outcome.
- High risk of bias: no blinding of outcome assessment, and the outcome measurement was likely to have been influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement was likely to be influenced by lack of blinding.

Incomplete outcome data (attrition bias due to amount, nature or handling of incomplete outcome data)

For each included study and/or each outcome, we described the completeness of data, including attrition and exclusions from the analyses. We stated whether the study reported attrition and exclusions, and reported the number of participants included in the analysis at each stage (compared with the number of randomised participants per intervention/comparator groups). We also noted if the study reported the reasons for attrition or exclusion and whether missing data were balanced across groups or were related to outcomes. We considered the implications of missing outcome data per outcome such as high dropout rates (e.g. above 15%) or disparate attrition rates (e.g. difference of 10% or more between study arms).

- Low risk of bias: no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to introduce bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes was not enough to have a clinically relevant impact on observed effect size; appropriate methods, such as multiple imputation, were used to handle missing data.
- Unclear risk of bias: insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias; the study did not address this outcome.
- High risk of bias: reason for missing outcome data was likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in the intervention effect estimate; for continuous outcome data, plausible effect size (mean difference or standardised mean difference) among missing outcomes enough to induce clinically-relevant bias in observed effect size; 'as-treated' or similar analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.

Selective reporting (reporting bias due to selective outcome reporting)

We assessed outcome reporting bias by integrating the results of the appendix 'Matrix of study endpoints (publications and trial documents)' (Boutron 2014; Jones 2015; Mathieu 2009), with those of the appendix 'High risk of outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) classification' (Kirkham 2010). This analysis formed the basis for the judgement of selective reporting.

- Low risk of bias: the study protocol was available and all the studies' prespecified (primary and secondary) outcomes that were of interest to this review were reported in the prespecified way; the study protocol was unavailable, but it was clear that the published reports included all expected outcomes (ORBIT classification).
- Unclear risk of bias: insufficient information about selective reporting.
- High risk of bias: not all the studies' prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; one or more reported primary outcomes were not prespecified (unless clear justification for their reporting was provided, such as an unexpected adverse effect); one or more outcomes of interest in the Cochrane Review were reported incompletely so that we cannot enter them in a meta-analysis; the study report failed to include results for a key outcome that we would expect to have been reported for such a study (ORBIT classification).

Other bias

- Low risk of bias: the study appears to be free from other sources of bias.
- Unclear risk of bias: there was insufficient information to assess whether an important risk of bias existed; insufficient rationale or evidence that an identified problem introduced bias.
- High risk of bias: the study had a potential source of bias related to the specific study design used; the study was claimed to be fraudulent; or the study had some other serious problem.

Appendix 3. Selection bias decisions

Selection bias decisions for studies reporting unadjusted analyses: comparison of results obtained using method details alone with results using method details and trial baseline information^a

Reported randomisation and allocation concealment methods	'Risk of bias' judgement using methods reporting	Information gained from study characteristics data	'Risk of bias' using baseline information and methods reporting
Unclear methods	Unclear risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited or no baseline details	Unclear risk
Would generate a truly random sample, with robust allocation concealment	Low risk	Baseline imbalances present for important prognostic variable(s)	Unclear risk^b
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Low risk
		No baseline details	Unclear risk
Sequence is not truly random, or allocation concealment is inadequate	High risk	Baseline imbalances present for important prognostic variable(s)	High risk
		Groups appear similar at baseline for all important prognostic variables	Low risk
		Limited baseline details, showing balance in some important prognostic variables ^c	Unclear risk
		No baseline details	High risk

^aTaken from [Corbett 2014](#); judgements highlighted in bold indicate situations in which the addition of baseline assessments would change the judgement about risk of selection bias, compared with using methods reporting alone.

^bImbalance identified that appears likely to be due to chance.

^cDetails for the remaining important prognostic variables are not reported.

Appendix 4. Description of interventions

Trial ID	Intervention(s) (route, frequency, total dose/day)	Intervention(s) appropriate as applied in a clin-	Comparator(s) (route, frequency, total dose/day)	Comparator(s) appropriate as applied in a clin-
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Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus (Review)

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(Continued)

		ical practice setting ^a	ical practice setting ^a	ical practice setting ^a
Alfawaz 2018	Metformin 500 mg twice a day plus standard advice on diet plus exercise	Yes	C1: intensive diet and exercise C2: diet plus exercise	Yes
PREVENT-DM 2017	Metformin 850 mg daily for the first month, thereafter 850 mg twice daily. If side effects, then dose reduction. Titrated to the highest tolerable dose with a maximum of 850 mg three times a day	Yes	C1: intensive diet and physical activity C2: diet plus exercise	Yes
Zeng 2013	Metformin 38 mg once daily. Diet plus exercise (no details)	Yes	C1: diet plus exercise C2: pioglitazone 38 mg once daily Diet plus exercise	Yes
Zhao 2013	Metformin 500 mg twice daily Education plus behaviour interventions, including diet control and increased physical activity (at least 30 minutes per day and at least 5 days per week)	Yes	Education plus behaviour interventions, including diet control and increased physical activity (at least 30 minutes per day and at least 5 days per week)	Yes
Iqbal Hydrie 2012	Metformin 500 mg twice daily plus intensive diet and physical activity	Yes	C1: intensive diet plus physical activity C2: standard medical advice	Yes
Liao 2012	Metformin from 250 mg, three times daily, adjusting the dose according to blood glucose, with the maximum 1500 mg daily	Yes	Acarbose from 50 mg three times daily with meals, adjusting the dose according to blood glucose, with the maximum 300 mg daily	Yes
Ji 2011	Metformin 500 mg, three times daily, after meals. Standard advice on diet plus exercise	Yes	C1: Intensive diet plus exercise; based on individual dietary habits, calories are determined according to age, height, actual weight, activity intensity and season. Patients were given a low-fat diet and a controlled diet. Patients were instructed to have a balanced diet and exercise (150 minutes per week). C2: diet plus exercise	Yes

(Continued)

<p>Lu 2010</p>	<p>Metformin 250 mg three times daily, according to tolerance, gradually reaching the target dose of 500 mg three times daily</p> <p>Lectures and leaflets were given to inform the prognosis and hazards of pre-diabetes, and scientific diet and exercise instructions were provided for each follow-up to promote a healthy lifestyle</p>	<p>Yes</p>	<p>By giving lectures and sending out leaflets to inform the prognosis and hazards of pre-diabetes, providing healthy diet and lifestyle guidance, referring to the dietary nutrition guidelines of China, and adjusting diet according to individual specific conditions to maintain a balanced nutritional status.</p> <p>The advice was:</p> <p>(1) variety of food, mainly cereals, with a combination of grains and grains;</p> <p>(2) eat more vegetables, fruits and potatoes;</p> <p>(3) daily intake of milk, beans and their preparation;</p> <p>(4) eat adequate amount of fish, poultry, eggs and lean meat;</p> <p>(5) reduce the amount of cooking oil, eat light diet with little salt, not too greasy and salty, including not too much smoke and animal oil food, daily adult salt to 6 g, eat less pickles, monosodium glutamate and other sodium-containing food;</p> <p>(6) reasonable allocation of three meals, snacks should be appropriate.</p> <p>Reduce calorie intake to maintain the ideal weight. Patients with a BMI < 25kg/m² were advised 30 Kcal/kg-day, with emphasis on alcohol and sugary soft drinks: patients with a BMI ≥ 25kg/m² were encouraged to lose 0.5 g to 1.0 kg per month until ideal body weight. Initiate, encourage family members to care, supervise the completion of dietary plan.</p> <p>At each follow-up, the participants were informed of dietary compliance.</p> <p>The exercise advice was as follows:</p> <p>(1) exercise prescription should consider the patient's individual factors such as gender, age, height, weight and living habits comprehensively;</p> <p>(2) principle of gradual progress and acting according to ability. The formulation of exercise prescription should be based on the patient's disease degree, physical condition to develop a long-term plan, step by step, not subjective assumptions, eager for quick success and instant benefit.</p> <p>In the exercise prescription a clear purpose should be stated, and use the degree of realisation of this purpose to measure and modify the exercise prescription.</p>	<p>Yes</p>
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(Continued)

Patients are required to engage in continuous aerobic exercise. Generally, after 30 minutes of exercise, blood glucose starts to supply energy to tissues, thus causing a drop in blood glucose. Moreover, studies have confirmed that the effect of moderate amount of exercise on blood glucose lasts for 12 months. 17 hours, so people with diabetes should exercise at least once a day, no less than 30 minutes at a time. According to the principles and contents of exercise prescription, the exercise group should take appropriate physical activities and adopt various forms according to the specific conditions of each person, such as walking, jogging, playing ball games, aerobics, taijiquan, etc. It is required that the exercise program should be 1 exercise unit per day, lasting at least 30 minutes, and at least 5 days per week.

At each follow-up, participants were informed about exercise compliance and urged to stick to the prescribed exercise regimen.

BIGPRO1 2009	Metformin, 850 mg tablet twice a day; diet plus exercise	Yes	Identical placebo tablet given twice a day; diet plus exercise	Yes
Chen 2009	Metformin 750 mg, three times daily All patients received behaviour changing with reference to diet and exercise therapy in the diabetes guidelines of China	Yes	All patients received behaviour changing with reference to diet and exercise therapy in the diabetes guidelines of China.	Yes
Jin 2009	Metformin 1000 mg twice or three times daily. Diet plus exercise (no details)	Yes	C1: diet plus exercise (no details) C2: rosiglitazone 4 mg, orally, once daily. Diet plus exercise (no details)	Yes
Li 2009	Metformin 500 mg once daily plus diet and exercise	Yes	Individualised diet and exercise and education	Yes
Wang 2009	Metformin 250 mg twice daily, with or after meals. Plus standard advice on diet and exercise	Yes	Diet plus exercise	Yes
IDPP-1 2006	I1: Metformin, 500 mg twice a day I2: Metformin, 500 mg twice a day plus inten-	Yes	C1: intensive diet and exercise C2: standard care	Yes

(Continued)

	sive diet and physical activity			
Maji 2005	Metformin 500 mg once daily plus diet and physical activity	Yes	C1: intensive diet and physical activity C2: rosiglitazone 2 mg daily plus diet and physical activity C3: acarbose 25 mg twice daily plus diet and physical activity	Yes
Fang 2004	Metformin 375 mg to 750 mg three times a day	Yes	C1: acarbose 75 mg to 150 mg three times a day C2: intensive diet plus exercise C3: diet and physical activity	Yes
DPP/DPPOS 2002	Metformin 850 mg twice a day plus standard diet and lifestyle advice	Yes	C1: intensive diet plus exercise: consumption of a healthy low-calorie, low-fat diet and to engage in physical activity of moderate intensity (such as brisk walking) for at least 150 minutes/week C2: placebo tablets given twice a day plus standard diet and lifestyle advice	Yes
Lu 2002	Metformin 750 mg three times daily. Health education (not described, assumed to be standard care)	Yes	C1: health education (not described, assumed to be standard care) C2: diet instruction (every 6 months). Health education C3: fibre diet, fibre (Litesse) 6 g, twice daily, take with meal. Provide fibre once a month. Health education	Yes
Li 1999	Metformin, 250 mg three times a day	Yes	C1: placebo administered with the same schedule as metformin	Yes
Papoz 1978	Metformin 850 mg, twice daily plus placebo, twice daily; overweight participants were recommended calorie restriction	Yes	C1: glibenclamide 2.0 mg, orally, twice daily and placebo, orally, twice daily. Overweight participants were recommended calorie restriction C2: placebo, orally, twice daily; overweight participants were recommended calorie restriction	Yes

^aThe term 'clinical practice setting' refers to the specification of the intervention/comparator as used in the course of a standard medical treatment (such as dose, dose escalation, dosing scheme, provision for contraindications and other important features)

BMI: body mass index; **C:** comparator; **I:** intervention.

Appendix 5. Baseline characteristics (I)

Trial ID	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up) ^a	Description of participants	Trial period (year to year)	Country	Setting	Ethnic groups (%)	Duration of being at risk for T2DM
Alfawaz 2018	I: metformin	1 year (1 year)	IFG	April 2013 - March 2017	Saudi Arabia	Outpatient	Saudi Arabian 100%	—
	C1: intensive diet plus exercise						Saudi Arabian 100%	—
	C2: standard care						Saudi Arabian 100%	—
PRE-VENT-DM 2017	I1: metformin	12 months (12 months)	IFG and/or moderately elevated HbA1c, Hispanic	2013 - 2015	USA	Outpatient	100% Hispanic	—
	C1: intensive diet plus exercise						100% Hispanic	—
	C2: standard care						100% Hispanic	—
Zeng 2013	I: metformin	2 years (2 years)	IFG with or without IGT, Chinese	January 2009 - March 2010 (recruitment period) 2012 (end of treatment period)	China	Outpatient	Chinese: 100	—
	C1: Standard care						Chinese: 100	—
	C2: pioglitazone						Chinese: 100	—
Zhao 2013	I: metformin plus intensive diet plus exercise	1 year (1 year)	IFG, IGT, obese, Chinese	—	China	Outpatient	Chinese: 100	—
	C: intensive diet plus exercise						Chinese: 100	—
Iqbal Hydrie 2012	I1: metformin plus intensive diet and exercise	18 months (18 months)	IGT, Asian	—	Pakistan	Outpatient	Assume 100% Asian (Pakistani)	—
	C1: intensive diet and exercise						Assume 100% Asian (Pakistani)	—
	C2: standard care						Assume 100% Asian (Pakistani)	—

Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus (Review)

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(Continued)

Liao 2012	I: metformin	1 year (1 year)	IGT, Chinese	August 2009 - July 2010 (recruitment period) 2011 (end of treatment period)	China	Outpatient	Chinese: 100	—
	C: acarbose						Chinese: 100	—
Ji 2011	I1: metformin	2 years (2 years)	IFG and/or IGT, Chinese	September 2007 - August 2008 (recruitment period) 2010 (end of treatment period)	China	Outpatient	Chinese: 100	—
	C1: intensive diet plus exercise						Chinese: 100	—
	C2: standard care						Chinese: 100	—
Lu 2010	I: metformin	2 years (2 years)	IFG and/or IGT, Chinese	September 2007 (recruitment point) 2009 (end of treatment point)	China	Outpatient	Chinese: 100	—
	C: standard care						Chinese: 100	—
BIGPRO1 2009	I: metformin	1 year (1 year)	Adults with IFG or IGT	January 1991- mid 1992	France	Outpatient	—	—
	C: placebo						—	—
Chen 2009	I: metformin	1 year (2 years)	IGT patients	—	China	Outpatient	Chinese: 100	—
	C: standard care						Chinese: 100	—
Jin 2009	I: metformin	3 years (3 years)	IFG patients	January 2004 - May 2006 (recruitment period) 2009 (end of treatment period)	China	Outpatient	Chinese: 100	—
	C1: standard care						Chinese: 100	—
	C2: rosiglitazone						Chinese: 100	—
Li 2009	I: metformin	3 years (3 years)	IFG and IGT, obese, Chinese	2004 - 2005 (recruitment period) 2008 (end of treatment period)	China	Outpatient	Chinese: 100	—
	C: intensive diet plus exercise						Chinese: 100	—
Wang 2009	I: metformin	1 year (1 year)	IFG, IGT or both, Chinese	January - December 2008 (recruitment period) 2009 (end of treatment period)	China	Outpatient	Chinese: 100	—
	C: standard care						Chinese: 100	—

(Continued)

IDPP-1 2006	I1: metformin	3 years (3 years)	Participants with IGT aged 35 years to 55 years	2001 - 2005	India	Outpatient	Asian Indian: 100	—
	I2: metformin plus intensive diet and physical activity						Asian Indian: 100	—
	C1: intensive exercise plus diet						Asian Indian: 100	—
	C2: standard care						Asian Indian: 100	—
Maji 2005	I1: metformin	3 years (3 years)	IGT	Initiated 2001	India	Outpatient	Assume 100% Indian	—
	C1: intensive lifestyle intervention						Assume 100% Indian	—
	C2: rosiglitazone						Assume 100% Indian	—
	C3: acarbose						Assume 100% Indian	—
Fang 2004	I: metformin	5 years (5 years)	IFG, IGT or both, Chinese	1998-2003	China	Outpatient	Assume 100% Asian (Chinese)	—
	C1: acarbose						Assume 100% Asian (Chinese)	—
	C2: intensive exercise and diet						Assume 100% Asian (Chinese)	—
	C3: standard care						Assume 100% Asian (Chinese)	—
DPP/DPPOS 2002	I: metformin	Mean 2.8 years (mean 15 years)	IGT and elevated fasting glucose. Overweight or obese	1996-1999 (recruitment period)	USA	Outpatient	White: 56	—
	C1: intensive exercise and diet			July 2001 (end of treatment period)			African American: 21 Hispanic: 15.1 American Indian: 4.8 Asian: 3.4	
				followed up in the DPP Outcomes Study (DPPOS 2002, to 2014)			White: 54	—
							African American: 19 Hispanic: 17 American Indian: 6 Asian: 5	

(Continued)

	C2: placebo						White: 54 African American: 20 Hispanic: 16 American Indian: 6 Asian: 5	—
Lu 2002	I1: metformin	3 year (3 years)	IGT, Chinese	—	China	Outpatient	Chinese: 100	—
	C1: standard care						Chinese: 100	—
	C2: standard care plus diet instruction every 6th month						Chinese: 100	—
	C3: standard care plus fibre diet						Chinese: 100	—
Li 1999 ^a	I: metformin	12 months (12 months)	IGT, Chinese	1992-1994	China	Outpatient	Assume 100% Asian (Chinese)	—
	C: placebo						Assume 100% Asian (Chinese)	—
Papoz 1978	I1: metformin (plus placebo)	24 months (26 months)	IFG, IGT or both	Participants entered the trial from 1969 to 1971	France	Outpatient	—	—
	C1: glibenclamide plus placebo						—	—
	C2: placebo						—	—

—: denotes not reported

^aBaseline data only available for the participants who completed the trial

C: comparator; **I:** intervention; **DPP:** Diabetes Prevention Program; **HbA1c:** glycosylated haemoglobin A1c; **IFG:** impaired fasting glucose; **IGT:** impaired glucose tolerance.

Appendix 6. Baseline characteristics (II)

Trial ID	Intervention(s) and comparator(s)	Sex (female %)	Age (mean/range years (SD))	Fasting plasma glucose (mean mmol/L (SD))	2h-PG (mean mmol/L (SD))	Indicator of increased risk: elevated HbA1c (mean % (SD))	BMI (mean kg/m ² (SD))	Comedications/Cointerventions	Comorbidities
Alfawaz 2018	I: metformin	71	42.6 (6.9)	6.6 (0.5)	—	5.6 (0.5)	32.1 (5.7)	—	—
	C1: intensive diet plus exercise	70	43.4 (7.8)	6.1 (0.4)	—	5.8 (0.4)	31.3 (6.4)	—	—
	C2: standard care	75	42.3 (11.2)	6.0 (0.4)	—	5.6 (0.5)	32.6 (5.8)	—	—
PRE-VENT-DM 2017	I1: metformin	100	45.8 (11.7)	5.3 (0.6)	—	6.0 (0.2)	33.2 (5.5)	—	—
	C1: intensive diet plus exercise	100	45.5 (12.3)	5.4 (0.4)	—	5.9 (0.3)	34.3 (7.9)	—	—
	C2: standard care	100	44.0 (13.6)	5.3 (0.6)	—	5.9 (0.2)	32.2 (5.7)	—	—
Zeng 2013	I: metformin	44	47.7 (5.8)	5.5 (0.4)	8.75 (0.57)	—	25.2 (1.8)	—	—
	C1: Standard care	42	48.6 (7.4)	5.6 (0.3)	8.9 (0.4)	—	25.3 (2.6)	—	—
	C2: pioglitazone	46	47.2 (4.4)	5.7 (0.2)	8.9 (0.6)	—	25.2 (3.2)	—	—
Zhao 2013	I: metformin plus intensive diet plus exercise	43	—	—	9.32 (1.51)	—	28.61 (3.5)	—	—
	C: intensive diet plus exercise	48	—	—	9.13 (1.72)	—	28.32 (3.7)	—	—
Iqbal Hydrie 2012	I1: metformin plus intensive diet and physical activity	—	43.5 (8.4)	—	—	—	28.1 (4.3)	Information about healthy diet and exercise	25% had hypertension at baseline
	C1: intensive diet and physical activity	—	43.1 (10.1)	—	—	—	26.1 (4.7)	—	—
	C2: standard care	—	44.2 (10.9)	—	—	—	27.0 (5.7)	—	—

(Continued)

Liao 2012	I: metformin	46	50.8 (9.3)	6.03 (0.5)	8.2 (0.84)	—	—	—	—
	C: acarbose	48	50.5 (8.3)	6.05 (0.51)	8.28 (1.12)	—	—	—	—
Ji 2011	I1: metformin	54	50.9 (2.7)	7.0 (1.4)	8.8 (1.3)	—	24.6 (2.8)	—	—
	C1: Intensive diet plus exercise	47	52.1 (2.3)	7.2 (0.7)	9.0 (1.5)	—	24.4 (1.4)	—	—
	C2: standard care	53	53.4 (3.8)	6.9 (1.8)	8.7 (1.3)	—	24.6 (2.8)	—	—
Lu 2010	I: metformin	43	41 (4.6)	—	—	5.87 (0.47)	25.1 (2.8)	—	—
	C: standard care	41	41 (4.3)	—	—	5.89 (0.44)	25.5 (3.4)	—	—
BIGPRO1 2009 ^a	I: metformin	76	52.6 (6.2)	5.8 (0.6)	8.3 (1.2)	—	33.5 (5.9)	Diet and exercise	—
	C: placebo	58	48.9 (6.7)	5.6 (0.8)	8.5 (1.2)	—	35.6 (7.5)	Diet and exercise	—
Chen 2009	I: metformin	41	56.4 (2.1)	5.4 (0.6)	9.1 (0.8)	—	127.2 (17.9)	—	—
	C: standard care	44	56.3 (12.8)	5.3 (0.6)	9.0 (0.9)	—	125.8 (18.0)	—	—
Jin 2009	I: metformin	—	—	6.47 (0.18)	6.82 (0.45)	—	23.95 (3.04)	—	—
	C1: standard care	—	—	6.47 (0.18)	6.92 (0.41)	—	24.8 (3.47)	—	—
	C2: rosiglitazone	—	—	6.5 (0.19)	6.88 (0.5)	—	24.85 (3.97)	—	—
Li 2009	I: metformin	—	—	6.6 (0.4)	10.4 (0.3)	—	28.1 (1.4)	—	—
	C: intensive diet plus exercise	—	—	6.6 (0.3)	10.3 (0.4)	—	28.2 (1.7)	—	—
Wang 2009	I: metformin	—	49 (9)	—	9.4 (1.6)	—	25.0 (1.0)	—	—
	C: standard care	—	50 (7)	—	9.2 (1.5)	—	26.0 (2.0)	—	—
IDPP-1 2006	I1: metformin	19.5	45.9 (5.9)	5.4 (0.8)	8.5 (0.7)	6.2 (0.6)	25.6 (3.7)	—	26.3% had hypertension at baseline
	I2: metformin plus intensive diet and physical activity	18.6	46.3 (5.7)	5.4 (0.8)	8.5 (0.7)	6.2 (0.6)	25.6 (3.3)	—	37.2% had hypertension

(Continued)

									tion at baseline
	C1: intensive exercise plus diet	21.8	46.1 (5.7)	5.4 (0.7)	8.5 (0.7)	6.1 (0.5)	25.7 (3.3)	—	31.6% had hypertension at baseline
	C2: standard care	23.5	45.2 (5.7)	5.5 (0.8)	8.6 (0.7)	6.2 (0.5)	26.3 (3.7)	—	32.4% had hypertension at baseline
Maji 2005	I1: metformin	Only reported for all groups: 64.1	—	5.7 (0.8)	8.7 (1.1)	7.5 (0.6)	28.2 (1.2)	Information about healthy diet and exercise	—
	C1: intensive lifestyle intervention			5.6 (0.9)	8.5 (1.3)	7.4 (0.3)	28.6 (1.2)	—	—
	C2: rosiglitazone			5.8 (0.9)	8.9 (0.9)	7.6 (0.5)	28.5 (1.2)	Information about healthy diet and exercise	—
	C3: acarbose			5.3 (0.7)	8.8 (2.0)	7.4 (0.6)	28.1 (1.4)	Information about healthy diet and exercise	—
Fang 2004	I: metformin	48	50 (1)	6.3 (2.1)	7.48 (1.9)	—	25.2 (0.4)	-	—
	C1: acarbose	50	50 (1)	6.5 (1.9)	8.38 (1.9)	—	24.9 (0.3)	-	—
	C2: intensive exercise and diet	40	49 (1)	5.6 (2.4)	6.99 (2.1)	—	25.3 (0.3)	-	—
	C3: standard care	40	47 (2)	5.7 (2.3)	6.35 (2.2)	—	24.8 (0.4)	-	—
DPP/DP-POS 2002	I: metformin	66.2	50.9 (10.3)	5.9 (0.5)	9.2 (0.9)	5.9 (0.5)	33.9 (6.6)	17% in all treatment groups had antihypertensive treatment at baseline.	16% of the women in both group had previously had gestational diabetes
	C1: intensive exercise and diet	68	50.6 (11.3)	5.90 (0.5)	9.1 (0.9)	5.91 (0.5)	33.9 (6.8)	5.2% of participants reported taking pharmacologic therapy for dyslipi-	
	C2: placebo	69	50.3 (10.4)	5.92 (0.5)	9.1 (1.0)	5.91 (0.5)	34.2 (6.8)		

daemia at entry to the trial

Overall 29.6% had a history of hypertension. 34% had a history of stroke. 16% had a history of revascularization. 32% had a history of myocardial infarction

(Continued)

Lu 2002	I1: metformin	25	61 (9)	—	9.0 (0.8)	—	26.1 (2.7)	—	—
	C1: standard care	16	65 (7)	—	9.1 (1.0)	—	25.9 (3.3)	—	—
	C2: standard care plus diet instruction every 6th month	35	63 (9)	—	9.0 (0.9)	—	26.0 (3.2)	—	—
	C3: standard care plus fibre diet	29	64 (9)	—	9.4 (0.9)	—	26.2 (3.0)	—	—
Li 1999 ^b	I: metformin	27.2	49 (1.3)	6.9 (0.9)	9.1 (0.9)	7.4 (0.8)	26.0 (23)	Information about healthy diet and exercise	—
	C: placebo	29.7	50 (1.1)	7.3 (1.0)	9.0 (1.0)	7.3(0.8)	26.4 (2.4)	Information about healthy diet and exercise	—
Papoz 1978	I1: metformin (plus placebo)	0	44 (5.5) ^c	6.7 (0.7) ^{c,d,e}	8.2 (1.7) ^{c,d,e}	—	—	Overweight participants were prescribed calorie restriction in order to approach their ideal body weight	—
	C1: glibenclamide plus placebo	0	43 (10.6) ^c	6.7 (0.7) ^{c,d,e}	8.8 (2.0) ^{c,d,e}	—	—	Overweight participants were prescribed calorie re-	—

(Continued)

							striction in order to approach their ideal body weight
C2: placebo	0	45 (5.7) ^c	6.3 (0.7) ^{c,d,e}	8.3 (2.1) ^{c,d,e}	—	—	Overweight participants were prescribed calorie restriction in order to approach their ideal body weight

—: denotes not reported

^aBaseline data only available for the people with IGT/IFG who completed the trial

^bBaseline data only available for the participants who completed the trial

^cSD calculated from standard error

^dGlucose concentrations were converted from mg/dL to mmol/L (diabetes.co.uk 2019a)

^eBlood glucose concentrations were converted to plasma glucose values (diabetes.co.uk 2019b)

BMI: body mass index; **C**: comparator; **CVD**: cardiovascular disease; **HbA1c**: glycosylated haemoglobin A1c; **I**: intervention; **SD**: standard deviation.

Appendix 7. Matrix of study endpoints (publications and trial documents)

Trial ID	
Alfawaz 2018	<p>Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published <u>design</u> paper)^{a,c}</p> <hr/> <p>Source: N/T</p> <hr/> <p>Endpoints quoted in publication(s)^{b,c}</p> <hr/> <p>Primary outcome measure(s): participants with metabolic syndrome</p> <p>Secondary outcome measure(s): individual components of metabolic syndrome</p> <p>Other outcome measure(s): total number of metabolic syndrome components; metabolic syndrome risk-score</p> <hr/> <p>Endpoints quoted in <u>abstract</u> of publication(s)^{b,c}</p> <hr/> <p>Primary outcome measure(s): participants with metabolic syndrome</p> <p>Secondary outcome measure(s): individual components of metabolic syndrome</p> <p>Other outcome measure(s): —</p>
PREVENT-DM 2017	<p>Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published <u>design</u> paper)^{a,c}</p> <hr/> <p>Source: NCT02088034</p> <p>Primary outcome measure(s): weight</p> <p>Secondary outcome measure(s): cardiometabolic markers, physical activity, dietary intake, diabetes knowledge (assessed with Spanish-speaking Diabetes Knowledge Questionnaire)</p> <p>Other outcome measure(s):</p> <p>Trial results available in trial register: yes</p> <hr/> <p>Endpoints quoted in publication(s)^{b,c}</p> <hr/> <p>Primary outcome measure(s): blood glucose, insulin levels</p> <p>Secondary outcome measure(s): —</p> <p>Other outcome measure(s): weight</p> <hr/> <p>Endpoints quoted in <u>abstract</u> of publication(s)^{b,c}</p> <hr/> <p>Primary outcome measure(s): weight loss</p> <p>Secondary outcome measure(s): HbA1c, waist circumference</p> <p>Other outcome measure(s):</p>
Zeng 2013	<p>Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published <u>design</u> paper)^{a,c}</p> <hr/> <p>Source: NT</p>

(Continued)

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}
Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting blood glucose, 2-hour plasma glucose

Other outcome measure(s): fasting insulin, 2-hour insulin, BMI, blood pressure, cholesterol, conversion to normoglycaemia

Endpoints quoted in abstract of publication(s)^{b,c}
Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting blood glucose, 2-hour plasma glucose

Other outcome measure(s): fasting insulin, 2-hour insulin, BMI, blood pressure, cholesterol, conversion to normoglycaemia

Zhao 2013

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}
Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}
Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting blood glucose, 2-hour plasma glucose, non-serious adverse events

Other outcome measure(s): fasting insulin, HOMA-IR, WHR, BMI

Endpoints quoted in abstract of publication(s)^{b,c}
Primary outcome measure(s): — (NA)

Secondary outcome measure(s): —

Other outcome measure(s): —

Iqbal Hydrie 2012

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}
Source: main publication

Primary outcome measure(s): —

(Continued)

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s):

Other outcome measure(s): waist circumference, weight changes

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s):

Other outcome measure(s):

Liao 2012

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM, serious adverse events

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): fasting insulin, HOMA-IR, WHR, BMI, conversion to normoglycaemia

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): —

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): —

Ji 2011

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

(Continued)

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose, HbA1c

Other outcome measure(s): conversion to normoglycaemia, BMI, triglycerides, cholesterol, hs-CRP, fasting insulin

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose, HbA1c

Other outcome measure(s): conversion to normoglycaemia, BMI, triglycerides, cholesterol, hs-CRP, fasting insulin

 Lu 2010

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM, serious adverse events

Secondary outcome measure(s): HbA1c (%), IGT, IFG, non-serious adverse events

Other outcome measure(s): BMI, compliance of treatment

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM, serious adverse events

Secondary outcome measure(s): HbA1c (%), IGT, IFG, non-serious adverse events

Other outcome measure(s): BMI, compliance of treatment

 BIGPRO1 2009

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: design paper

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): —

Secondary outcome measure(s): —

(Continued)

Other outcome measure(s): not prioritised as primary or secondary: fasting plasma glucose; 2-hour plasma glucose; plasma lipids: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides; fasting plasma insulin; 2-hour plasma insulin; blood pressure: systolic and diastolic blood pressure; BMI and WHR

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): not prioritised as primary or secondary: fasting plasma glucose; 2-hour plasma glucose; plasma lipids: total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides; fasting plasma insulin; 2-hour plasma insulin; blood pressure; BMI and WHR

Chen 2009

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): reversion to normoglycaemia

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): —

Jin 2009

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM, serious adverse event

(Continued)

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose, non-serious adverse event

Other outcome measure(s): fasting plasma insulin, 2-hour plasma insulin, BMI, reversion to normoglycaemia

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): fasting plasma insulin, 2-hour plasma insulin

Li 2009

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): fasting insulin, BMI, leptin, triglycerides

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): fasting insulin, BMI, leptin, triglycerides

Wang 2009

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): 2-hour plasma glucose, non-serious adverse events

(Continued)

Other outcome measure(s): fasting blood glucose

Endpoints quoted in abstract of publication(s)^{b,c}
Primary outcome measure(s): — (NA)

Secondary outcome measure(s): —

Other outcome measure(s): —

IDPP-1 2006

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}
Source: [NCT00279240](#)
Primary outcome measure: incidence of T2DM

Secondary outcome measure: benefits of the drug on anthropometric variables and biochemical parameter

Other outcome measure(s): —

Trial results available in trial register: yes

Endpoints quoted in publication(s)^{b,c}
Primary outcome measure(s): morbidity of T2DM

Secondary outcome measure(s): mortality; morbidity of cardiovascular disease; fasting and 2-hour plasma glucose; plasma lipids: total cholesterol, LDL cholesterol and HDL cholesterol; blood pressure; BMI; adverse events; costs

Other outcome measure(s): —

Endpoints quoted in abstract of publication(s)^{b,c}
Primary outcome measure: incidence of T2DM

Secondary outcome measure(s): diabetes related morbidity, adverse events, all-cause mortality, total cholesterol, LDL cholesterol and HDL cholesterol, blood pressure, BMI, socioeconomic effects

Other outcome measure(s): —

Maji 2005

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}
Source: main publication

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}
Primary outcome measure(s): —

Secondary outcome measure(s): —

(Continued)

Other outcome measure(s): not described whether outcomes were primary or secondary: incidence of T2DM, per cent change in glycaemic measures

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): not described whether outcomes were primary or secondary: conversion to normoglycaemia

Fang 2004

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: N/T

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM, all-cause mortality, serious adverse events

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose, non-serious adverse events

Other outcome measure(s): BMI, total cholesterol, triglycerides, conversion to normoglycaemia

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): conversion to normoglycaemia

DPP/DPPOS 2002

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

DPP: Source: [NCT00004992](#); design article and protocol available from website ([DPP/DPPOS 2002](#))

Primary outcome measure(s): incidence of T2DM

DPPOS: Source: [NCT00038727](#); design article and protocol available from website ([DPP/DPPOS 2002](#))

Primary outcome measure(s): incidence of T2DM; aggregate microvascular complications

DPP: Secondary outcome measure(s): HbA1c; insulin and glucose; electrocardiogram; cardiovascular symptom assessment; blood pressure; carotid ultrasound; lipoproteins; fibrinolysis and clotting factors; albumin excretion; physical measurements; physical activity; nutrient intake; health-related quality of life; resource utilisation; safety

DPPOS: Secondary outcome measure(s): microvascular and cardiovascular disease risk factors; microvascular and cardiovascular disease risk factors; subclinical atherosclerosis; quality of life and economic analyses, bone density, health aging index; pulmonary function, urinary incontinence, amputation of lower extremity, hospitalisations; cardiovascular disease events

Other outcome measure(s): quote: "...comparing the incidence and determinants of these health outcomes in participants with new-onset diabetes and IGT, as well as assessing subgroups of participants in order to evaluate the effect of age, race/ethnicity, and sex on health outcomes"

Trial results available in trial register: no trial results available, but references to publications at [clinicaltrials.gov](#)

(Continued)

Endpoints quoted in publication(s)^{b,c}

DPP: Primary outcome measure(s): incidence of T2DM

DPPOS: Primary outcome measure(s): incidence of T2DM; aggregate microvascular complications

DPP: Secondary outcome measure(s): HbA1c; insulin and glucose; electrocardiogram; cardiovascular symptom assessment; blood pressure; lipoproteins; fibrinolysis and clotting factors; albumin excretion; physical measurements; physical activity; nutrient intake; health-related quality of life; resource utilisation; safety

DPPOS: Secondary outcome measure(s): microvascular and cardiovascular disease risk factors; economic analyses; health aging index; urinary incontinence

Other outcome measure(s): several subgroup analyses investigating the incidence of the primary outcomes

Endpoints quoted in abstract of publication(s)^{b,c}

DPP: Primary outcome measure(s): incidence of T2DM

DPPOS: Primary outcome measure(s): incidence of T2DM; aggregate microvascular complications

DPP: Secondary outcome measure(s): insulin; cardiovascular symptom assessment; blood pressure; lipoproteins; fibrinolysis and clotting factors; albumin excretion; physical measurements; nutrient intake; health related quality of life; resource utilisation

DPPOS: Secondary outcome measure(s): microvascular and cardiovascular disease risk factors; economic analyses; health aging index; urinary incontinence

Other outcome measure(s): several subgroup analyses investigating the incidence of the primary outcomes

Lu 2002

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}

Source: NT

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): —

Trial results available in trial register: —

Endpoints quoted in publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM, serious adverse events

Secondary outcome measure(s): fasting plasma glucose, 2-hour plasma glucose

Other outcome measure(s): 1 hour PG

Endpoints quoted in abstract of publication(s)^{b,c}

Primary outcome measure(s): incidence of T2DM

Secondary outcome measure(s): fasting blood sugar, - hour plasma glucose

(Continued)

Other outcome measure(s): 1 hour plasma glucose

Li 1999

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}
Source: main publication

Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): not described whether outcomes were primary or secondary: incidence of T2DM, weight, lipids, risk factors for cardiovascular disease

Trial results available in trial register: no

Endpoints quoted in publication(s)^{b,c}
Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): not described whether outcomes were primary or secondary: glycaemic control: fasting and 2-hour plasma glucose, HbA1c; plasma lipids: total cholesterol and triglycerides; fasting and 2-hour plasma insulin; blood pressure: Systolic and diastolic blood pressure; BMI and WHR; adverse events

Endpoints quoted in abstract of publication(s)^{b,c}
Primary outcome measure(s): —

Secondary outcome measure(s): —

Other outcome measure(s): not described whether outcomes were primary or secondary: incidence of T2DM, adverse events, HbA1c, total cholesterol and triglycerides, fasting plasma insulin, blood pressure, weight change

Papoz 1978

Endpoints quoted in trial document(s) (ClinicalTrials.gov, FDA/EMA document, manufacturer's website, published design paper)^{a,c}
Source: N/T

Endpoints quoted in publication(s)^{b,c}
Primary outcome measure(s): blood glucose, insulin levels

Secondary outcome measure(s): —

Other outcome measure(s): weight

Endpoints quoted in abstract of publication(s)^{b,c}
Primary outcome measure(s): blood glucose, insulin levels

Secondary outcome measure(s): —

Other outcome measure(s): weight

— denotes not reported

^aTrial document(s) refers to all available information from published design papers and sources other than regular publications (e.g. FDA/EMA documents, manufacturer's websites, trial registers).

(Continued)

^bPublication(s) refers to trial information published in scientific journals (primary reference, duplicate publications, companion documents or multiple reports of a primary trial)

^cPrimary and secondary outcomes refer to verbatim specifications in publication/records. Unspecified outcome measures refer to all outcomes not described as primary or secondary outcome measures

BMI: body mass index; **CRP:** C-reactive protein; **EMA:** European Medicines Agency; **FDA:** Food and Drug Administration (US); **HDL:** high-density lipoprotein; **HOMA-IR:** homeostatic model assessment insulin resistance; **hs-CRP:** high sensitive C-reactive protein; **IFG:** impaired fasting glucose; **IGT:** impaired glucose tolerance; **LDL:** low-density lipoprotein; **NT:** no trial document available; **NA:** no abstract available; **PG:** plasma glucose; **T2DM:** type 2 diabetes mellitus; **WHR:** waist-to-hip ratio.

Appendix 8. High risk of outcome reporting bias according to Outcome Reporting Bias In Trials (ORBIT) classification

Trial ID	Outcome	High risk of bias (category A) ^a	High risk of bias (category D) ^b	High risk of bias (category E) ^c	High risk of bias (category G) ^d
Alfawaz 2018	Incidence of T2DM	No	No	No	Yes
	Adverse events	No	No	No	Yes
PREVENT-DM 2017	Hypoglycaemia	No	No	Yes	No
Zeng 2013	Incidence of T2DM	No	No	No	No
	Measures of blood glucose control	No	No	No	No
Zhao 2013	Incidence of T2DM	No	No	No	No
	Non-serious adverse events	No	No	Yes	No
	Measures of blood glucose control	No	No	No	No
Liao 2012	Incidence of T2DM	No	No	No	No
	Serious adverse events	No	No	No	No
	Measures of blood glucose control	No	No	No	No
Iqbal Hydrie 2012	Hypoglycaemia	No	Yes	No	No
	Adverse events	No	Yes	No	No
Ji 2011	Incidence of T2DM	No	No	No	No
	Serious adverse events	No	No	No	No
	Measures of blood glucose control	No	No	No	No
Lu 2010	Incidence of T2DM	No	No	No	No

(Continued)

	Serious adverse events	No	No	No	No
	Non-serious adverse events	No	No	No	No
	Measures of blood glucose control	No	No	No	No
BIGPRO1 2009	Incidence of T2DM	No	Yes	No	No
	Hypoglycaemia	No	Yes	No	No
	Adverse events	No	Yes	No	No
Chen 2009	Incidence of T2DM	No	No	No	No
	Non-serious adverse events	No	No	Yes	No
	Measures of blood glucose control	No	No	No	No
Jin 2009	Incidence of T2DM	No	No	No	No
	Serious adverse events	No	No	No	No
	Non-serious adverse events	No	No	No	No
	Measures of blood glucose control	No	No	No	No
Li 2009	Incidence of T2DM	No	No	No	No
	Measures of blood glucose control	No	No	No	No
Wang 2009	Incidence of T2DM	No	No	No	No
	Non-serious adverse events	No	No	No	No
	Measures of blood glucose control	No	No	No	No
IDPP-1 2006	Serious adverse events	No	Yes	No	No
	Non-fatal myocardial infarction	No	Yes	No	No
	Stroke	No	Yes	No	No
	Non-serious adverse events	No	No	Yes	No
Maji 2005	Hypoglycaemia	No	Yes	No	No
	Adverse events	No	Yes	No	No
Fang 2004	All-cause mortality	No	No	No	No
	Incidence of T2DM	No	No	No	No
	Serious adverse events	No	No	No	No
	Non-serious adverse events	No	No	No	No

(Continued)

	Measure of blood glucose control	No	No	No	No
DPP 2002	Serious adverse events	No	Yes	No	No
	Non-fatal myocardial infarction	No	No	Yes	No
	Non-fatal stroke	No	No	Yes	No
	Non-serious adverse events	No	Yes	No	No
	Hypoglycaemia	No	Yes	No	No
Lu 2002	Incidence of T2DM	No	No	No	No
	Serious adverse events	No	No	No	No
	Measures of blood glucose control	No	No	No	No
Li 1999	Hypoglycaemia	No	Yes	No	No
Papoz 1978	Adverse events	No	No	No	Yes

^aClear that outcome was measured and analysed; trial report states that outcome was analysed but only reports that result was not significant

(Classification 'A', table 2, [Kirkham 2010](#))

^bClear that outcome was measured and analysed; trial report states that outcome was analysed but no results reported

(Classification 'D', table 2, [Kirkham 2010](#))

^cClear that outcome was measured; clear that outcome was measured but not necessarily analysed; judgement says likely to have been analysed but not reported because of non-significant results

(Classification 'E', table 2, [Kirkham 2010](#))

^dUnclear whether the outcome was measured; not mentioned but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results

(Classification 'G', table 2, [Kirkham 2010](#))

ORBIT: Outcome Reporting Bias In Trials

Appendix 9. Definition of endpoint measurement (I)^a

Trial ID	All-cause mortality	Development of type 2 diabetes mellitus	Serious adverse events	Cardiovascular mortality	Non-fatal myocardial infarction	Non-fatal stroke	Amputation of lower extremity
Alfawaz 2018	NI	NI	NI	NI	NI	NI	NI
PREVENT-DM 2017	NI	Type 2 diabetes mellitus IO	NI	NI	NI	NI	NI
Zeng 2013	NR	ND IO	NR	NR	NR	NR	NR
Zhao 2013	NR	ND IO	NR	NR	NR	NR	NR
Iqbal Hydrie 2012	NI	Either fasting plasma glucose of > 125 mg/dL (6.9 mmol/L) and/or 2-hour plasma glucose of > 199 mg/dL (11.1 mmol/L) IO	NI	NI	NI	NI	NI
Liao 2012	NR	ND IO	NR	NR	NR	NR	NR
Ji 2011	NR	ND IO	NR	NR	NR	NR	NR
Lu 2010	NR	American Diabetes Association 1997 criteria (any glucose \geq 11.1 mmol/L or fasting plasma glucose \geq 7.0 mmol/L). Quote: "If the patient has diabetes symptoms such as polydipsia, polyuria and polyphagy, if FPG \geq 7.0mmol/L or 2hPG > 11.1mmol/L after meal, the second FPG and/or 75 g OGTT were performed within 6 weeks. If the diabetes crite-	NR	NR	NR	NR	NR

(Continued)

		ria were met, the primary study objective end-point was determined and the study was terminated."						
		IO						
BIGPRO1 2009	NI	NI	NI	NI	NI	NI	NI	NI
Chen 2009	NR	75 g OGTT, and confirmed with a repeated test (no other data)	NR	NR	NR	NR	NR	NR
		Quote: "If the results of 75g OGTT for 2 times during the observation were diabetic, they were considered to have converted to diabetes, which was the end point of the study."						
		IO						
Jin 2009	NR	ND	NR	NR	NR	NR	NR	NR
		IO						
Li 2009	NR	ND	NR	NR	NR	NR	NR	NR
		IO						
Wang 2009	NR	ND	NR	NR	NR	NR	NR	NR
		IO						
IDPP-1 2006	IO	WHO 1999 (either a fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL) and/or a 2-hour plasma glucose concentration ≥ 11.1 mmol/L (≥ 200 mg/dL), and confirmed with a repeat test)	IO	NI	NI	NI	NI	NI
		IO						
Maji 2005	NI	Type 2 diabetes mellitus	NI	NI	NI	NI	NI	NI
		IO						
Fang 2004	NR	ND	NR	NR	NR	NR	NR	NR

		(Continued)							
	DPP/DPPOS 2002	IO	American Diabetes Association criteria (fasting plasma glucose level \geq 126 mg/dL [7.0 mmol/L] or 2-hour plasma glucose \geq 200 mg/dL [11.1 mmol/L] after a 75 g OGTT, and confirmed with a repeated test) IO	Quote: "Serious adverse events have been defined to include any adverse experience occurring at any dose that results in any of the following outcomes: • Death • A life-threatening adverse experience • Inpatient hospitalization or prolongation of existing hospitalization • A persistent or significant disability/incapacity; or • A congenital anomaly/birth defect" IO	Quote:"CVD-related deaths" IO	NI	NI	NI	NI
	Lu 2002	NR	75 g OGTT, and confirmed with a repeated test (no other data) Quote: "If the results of 75 g OGTT at one time during the observation were diabetic, the patients were still treated according to the original regimen; if the patients were still diabetic at the next review, the patients were judged to have converted to diabetes, which was the end point of the study. If it is IGT or normal glucose tolerance, observation will be continued, and final results of each subject will be judged after review at the end of 3 years." IO	NR	NR	NR	NR	NR	NR

(Continued)

Li 1999	NI	Not described, presumable WHO 1985 criteria (either a fasting plasma glucose \geq 140 mg/dL (7.8 mmol/L) or higher or a 2-hour plasma glucose \geq 200 mg/dL (11.1 mmol/L) after a 75 g OGTT)	NI	NI	NI	NI	NI
		IO					
Papoz 1978	NI	NI	NI	NI	NI	NI	NI

^aIn addition to definition of endpoint measurement, description who measured the outcome (**AO**: adjudicated outcome measurement; **IO**: investigator-assessed outcome measurement; **SO**: self-reported outcome measurement)

2hPG: 2-hour plasma glucose; **CVD**: cardiovascular disease; **FPG**: fasting plasma glucose; **IGT**: impaired glucose tolerance; **ND**: not defined; **NI**: not investigated; **NR**: not reported; **OGTT**: oral glucose tolerance test; **WHO**: World Health Organization.

Appendix 10. Definition of endpoint measurement (II)^b

Trial ID	Blindness or severe vision loss	End-stage renal disease	Nonserious adverse events	Hypoglycaemic events	Health-related quality of life	Time to progression to T2DM	Measures of blood glucose control	Socioeconomic effects
Alfawaz 2018	NI	NI	NI	NI	NI	NI	Fasting blood glucose IO	NI
PRE-VENT-DM 2017	NI	NI	Adverse events SO	NI	NI	NI	HbA1c; fasting plasma glucose IO	NI
Zeng 2013	NR	NR	NR	NR	NR	NR	Fasting plasma glucose, 2-hour plasma glucose; Quote:" At the end, OGTT was used to judge the number of cases of NGT, IGR and DM. Biochemical detection was conducted by Olympus automatic biochemical instrument, glucose detection by glucose oxidase method, and insulin detection by radioimmunoassay." (no details) IO	NR
Zhao 2013	NR	NR	Damage of liver, kidney function	NR	NR	NR	Fasting blood glucose, 2-hour plasma glucose ND IO	NR
Iqbal Hydrie 2012	NI	NI	NI	NI	NI	NI	NI	NI
Liao 2012	NR	NR	NR	NR	NR	NR	Fasting plasma glucose, 2-hour plasma glucose; Quote:"At the initial visit, fasting 10-12h overnight, venous blood was taken and plasma glucose (i.e., FPG and 2hPG) was measured after OGTT (75g glucose). The above examination was repeated every 3 months.	NR

(Continued)

							Blood glucose was measured by hexokinase method (the biochemical instrument was automatic erab-xl-600)." (no more detail)	
							IO	
Ji 2011	NR	NR	NR	NR	NR	NR	Fasting plasma glucose, HbA1c, 2-hour plasma glucose	NR
							Quote:"All cases were followed for 2 years, outpatient follow-up once every 2 months, patients with glucose oxidase method is used to determination of FPG, 2h postprandial blood glucose (2 HPG), treatment before and after the treatment, test weight, height, and calculate the BMI, waist circumference, hip circumference, waist-to-hip ratio calculation, the determination of FPG, FINS application of chemiluminescence analysis, application of biochemical analyzer determination of TC, TG, LDL cholesterol (LDL - C), immune turbidimetric method is used to test the hs CRP, glycosylated hemoglobin (HbA1c) levels, Meanwhile, ISI =1/ (determined value of FINS ×FPG) was calculated. Review OGTT at the end of treatment to determine if diabetes has developed."	
							IO	
Lu 2010	NR	NR	Harmful and unexpected reactions of a drug under normal usage or dosage to prevent, diagnose, treat, or regulate physiological functions	NR	NR	NR	Fasting plasma glucose; 2-hour plasma glucose; HbA1c	NR
							Quote:"Venous blood was collected 8-12 hours after fasting, and serum was isolated for determination of blood glucose, total cholesterol, triglyceride HDL and LDL. Blood at finger tips was used to determine glycosylated hemoglobin (DS). 5 glycosylated hemoglobin analyzer).",	
							Quote:"Oral glucose tolerance test. On the morning of fasting venous blood sampling, 300ml sugar water containing 75g glucose was drunk within 5 minutes, and blood glucose was measured by venous blood sampling 2 hours later."	

(Continued)

							IO	
BIGPRO1 2009	NI	NI	NI	NI	NI	NI	2-hour plasma glucose; fasting plasma glucose	NI
							IO	
Chen 2009	NR	NR	NR	NR	NR	NR	Fasting plasma glucose, 2-hour plasma glucose;	NR
							ND	
							IO	
Jin 2009	NR	NR	NR	NR	NR	NR	Fasting plasma glucose, 2-hour plasma glucose;	NR
							ND	
							Quote:"Blood glucose was detected by tetokinase method"	
							IO	
Li 2009	NR	NR	NR	NR	NR	NR	Fasting plasma glucose, 2-hour plasma glucose;	NR
							ND	
							IO	
Wang 2009	NR	NR	ND	NR	NR	NR	Fasting blood glucose, 2-hour plasma glucose;	NR
							ND	
							IO	
IDPP-1 2006	NI	NI	NI	Hypoglycaemia	NI	NI	2-hour plasma glucose; fasting plasma glucose	NI
				SO, IO			IO	
Maji 2005	NI	NI	NI	NI	NI	NI	2-hour plasma glucose; HbA1c; fasting plasma glucose	NI
							IO	

(Continued)

Fang 2004	NR	NR	NR	NR	NR	NR	NR	Fasting plasma glucose; 2-hour plasma glucose; ND IO	NR
DPP/DPPOS 2002	NI	NI	NI	NI	NI	36-Item Short-Form (SF-36) health survey SO	NI	2-hour plasma glucose; HbA1c; Fasting plasma glucose IO	"The direct costs of medical care received outside the study and indirect costs were determined annually from patient self-report. Direct non-medical costs were assessed once during DPP and once during DPPOS, and costs were annualized. All costs were adjusted to 2000 or 2010 U.S. dollars using the Consumer Price Index and the Medical Consumer Price Index." IO
Lu 2002	NR	NR	NR	NR	NR	NR	NR	Fasting blood glucose, 1h plasma glucose, 2-hour plasma glucose	NR

(Continued)

								ND	
								IO	
Li 1999	NI	NI	NI	NI	NI	NI	NI	2-hour plasma glucose; HbA1c; fasting plasma glucose	NI
								IO	
Papoz 1978	NI	NI	NI	NI	NI	NI	NI	Fasting blood glucose, 2-hour glucose levels	NI
								IO	

^aIn addition to definition of endpoint measurement, description who measured the outcome (**AO**: adjudicated outcome measurement; **IO**: investigator-assessed outcome measurement; **SO**: self-reported outcome measurement)

BMI: body mass index; **CRP**: C-reactive protein; **FINS**: fasting insulin; **FPG**: fasting plasma glucose; **HbA1c**: glycosylated haemoglobin A1c; **ISI**: insulin sensitivity index; **ND**: not defined; **NI**: not investigated; **NR**: not reported; **OGTT**: oral glucose tolerance test.

Appendix 11. Adverse events (I)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Deaths (N)	Deaths(%)	Participants with at least one adverse event (N)	Participants with at least one adverse event (%)	Participants with at least one severe/serious adverse event (N)	Participants with at least one severe/serious adverse event (%)
Alfawaz 2018	I: metformin	59	—	—	—	—	—	—
	C1: intensive diet plus exercise	73	—	—	—	—	—	—
	C2: standard care	85	—	—	—	—	—	—
PRE-VENT-DM 2017	I1: metformin	29	0	0	10	34.4	0	0
	C1: intensive diet plus exercise	33	0	0	0	0	0	0
	C2: standard care	30	0	0	0	0	0	0
Zeng 2013	I: metformin	68	—	—	—	—	—	—
	C1: Standard care	66	—	—	—	—	—	—
	C2: pioglitazone	70	—	—	—	—	—	—
Zhao 2013	I: metformin plus intensive diet plus exercise	45	—	—	Gastrointestinal symptoms: 1	Gastrointestinal symptoms: 2.2	—	—
	C: intensive diet plus exercise	46	—	—	Gastrointestinal symptoms: 0	Gastrointestinal symptoms: 0	—	—
Iqbal Hydrie 2012	I1: metformin plus intensive diet and physical activity	95	0	0	—	—	—	—
	C1: intensive diet and physical activity	114	0	0	—	—	—	—

(Continued)

	C2: standard care	108	2	1.9	—	—	—	—
Liao 2012	I: metformin	51	—	—	—	—	Cerebral haemorrhage: 1	Cerebral haemorrhage: 2.0
	C: acarbose	50	—	—	—	—	Lung cancer: 1 hepatitis: 1	Lung cancer: 2.0 hepatitis: 2.0
Ji 2011	I1: metformin	52	—	—	—	—	—	—
	C1: Intensive diet plus exercise	60	—	—	—	—	—	—
	C2: standard care	64	—	—	—	—	—	—
Lu 2010	I: metformin	115	—	—	Diarrhoea: 11 nausea: 14 vomiting: 7 abdominal distension: 11 weak: 17 indigestion: 15 abdominal discomfort and headache: 8 abnormal defecate: 16 low blood sugar: 4 muscle pain: 2 dizzy: 7 rash: 1 sweating increases: 2 taste abnormalities: 13 chest discomfort: 2 flu symptoms: 1 weight loss, etc: 33	Diarrhoea: 9.5 nausea: 12 vomiting: 6.1 abdominal distension: 9.5 weak: 14.8 indigestion: 13 abdominal discomfort and headache: 7.0 abnormal defecate: 13.9 low blood sugar: 3.5 muscle pain: 6.1 dizzy: 0.8 rash sweating increases: 1.7 taste abnormalities: 11.3 chest discomfort: 1.7 flu symptoms: 0.8 weight loss, etc: 28.7	—	—
	C: standard care	111	—	—	Diarrhoea: 7 nausea: 5 vomiting: 5	Diarrhoea: 6.3 nausea: 4.5 vomiting: 4.5	—	—

(Continued)

					abdominal distension: 6 weak: 15 indigestion: 15 abdominal discomfort and headache: 3 abnormal defecate: 4 low blood sugar: 2 muscle pain: 0 dizzy: 8 rash: 0 sweating increases: 2 taste abnormalities: 1 chest discomfort: 1 flu symptoms: 2 weight loss, etc: 10	abdominal disten- sion: 5.4 weak: 13.5 indigestion: 13.5 abdominal discom- fort and headache: 2.7 abnormal defecate: 3.6 low blood sugar: 1.8 muscle pain: 0 dizzy: 7.2 rash: 0 sweating increases: 1.8 taste abnormalities: 0.9 chest discomfort: 0.9 flu symptoms: 1.8 weight loss, etc: 9		
BIGPRO1 2009	I: metformin	21	—	—	—	—	—	—
	C: placebo	36	—	—	—	—	—	—
Chen 2009	I: metformin	44	—	—	—	—	—	—
	C: standard care	46	—	—	—	—	—	—
Jin 2009	I: metformin	45	—	—	Hypoglycaemia 0	Hypoglycaemia 0	Severe gas- trointestinal reactions: 3	Severe gas- trointestinal reactions: 6.7
	C1: standard care	41	—	—	Hypoglycaemia 0	Hypoglycaemia 0	—	—
	C2: rosiglitazone	41	—	—	Facial oedema: 1 intolerance of both lower limbs: 2 hypoglycaemia: 0	Facial oedema: 2.4 intolerance of both lower limbs: 4.9 hypoglycaemia: 0	0	0
Li 2009	I: metformin	77	—	—	—	—	—	—

(Continued)

	C: intensive diet plus exercise	83	—	—	—	—	—	—
Wang 2009	I: metformin	30	—	—	Gastrointestinal symptoms: 2	Gastrointestinal symptoms: 6.7	—	—
	C: standard care	32	—	—	—	—	—	—
IDPP-1 2006	I1: metformin	128	0	0	—	0	—	—
	I2: metformin plus intensive diet and physical activity	121	1	0.8	—	—	—	—
	C1: intensive exercise plus diet	120	1	0.8	—	—	—	—
	C2: standard care	133	1	0.8	—	—	—	—
Maji 2005	I1: metformin	—	—	—	—	—	—	—
	C1: intensive lifestyle intervention	—	—	—	—	—	—	—
	C2: rosiglitazone	—	—	—	—	—	—	—
	C3: acarbose	—	—	—	—	—	—	—
Fang 2004	I: metformin	44	1	2.3	Diarrhea: 3	Diarrhea: 6.8	Death (liver cancer): 1	Death (liver cancer): 2.3
	C1: acarbose	45	0	0	Abdominal distension and diarrhoea: 3 rash: 1 frequent venting: 1	Abdominal distension and diarrhoea: 6.7 rash: 2.2 frequent venting: 2.2	—	—
	C2: intensive exercise and diet	36	0	0	0	0	0	0
	C3: standard care	35	0	0	0	0	0	0

(Continued)

DPP/DPPOS 2002	I: metformin	1073	6	0.6	Musculoskeletal symptoms: 20.0 events/100 person years ^a gastrointestinal symptoms: 77.8 events/100 person years	Musculoskeletal symptoms: — gastrointestinal symptoms: —		
	C1: intensive exercise and diet	1079	3	0.3	Musculoskeletal symptoms: 24.1 events/100 person years gastrointestinal symptoms: 12.9 events/100 person years	Musculoskeletal symptoms: — gastrointestinal symptoms: —	—	—
	C2: placebo	1082	5	0.5	Musculoskeletal symptoms: 21.1 events/100 person years gastrointestinal symptoms: 30.7 events/100 person years	Musculoskeletal symptoms: — gastrointestinal symptoms: —	—	—
Lu 2002	I1: metformin	80	—	—	—	—	—	—
	C1: standard care	75	1	1.3	—	—	Death (cerebral thrombosis with pulmonary infection): 1	Death (cerebral thrombosis with pulmonary infection): 1.3
	C2: standard care plus diet instruction every 6th month	64	—	—	—	—	—	—
	C3: standard care plus fibre diet	51	—	—	—	—	Stomach cancer: 1	Stomach cancer: 2.0
Li 1999	I: metformin	33	0	0	(1) Mild diarrhoea and nausea: 3	(1) 9.1	—	—
	C: placebo	37	0	0	(1) Mild nausea: 6	(1) 16	—	—

(Continued)

					(2) raised liver enzymes: 1	(2) 2.7		
Papoz 1978	I1: metformin (plus placebo)	—	—	—	—	—	—	—
	C1: glibenclamide plus placebo	—	—	—	—	—	—	—
	C2: placebo	—	—	—	—	—	—	—

—: denotes not reported

^aAll adverse events from DPP are calculated from number of events/100 person years; some participants might have experienced more than one event. Therefore only the number of participants with an event cannot be calculated

C: comparator; **I:** intervention.

Appendix 12. Adverse events (II)

Trial ID	Intervention(s) and comparator(s)	Parti- pants in- cluded in analysis (N)	Parti- pants dis- continuing trial due to an adverse event (N)	Parti- pants dis- continuing trial due to an adverse event (%)	Parti- pants with at least one hospitalisa- tion (N)	Parti- pants with at least one hospitalisa- tion (%)	Parti- pants with at least one outpatient treatment (N)	Parti- pants with at least one outpatient treatment (%)
Alfawaz 2018	I: metformin	59	—	—	—	—	—	—
	C1: intensive diet plus exercise	73	—	—	—	—	—	—
	C2: standard care	85	—	—	—	—	—	—
PRE- VENT-DM 2017	I1: metformin	29	1	3.4	—	—	—	—
	C1: intensive diet plus exercise	33	0	0	—	—	—	—
	C2: standard care	30	0	0	—	—	—	—
Zeng 2013	I: metformin	68	—	—	—	—	—	—
	C1: Standard care	66	—	—	—	—	—	—
	C2: pioglitazone	70	—	—	—	—	—	—
Zhao 2013	I: metformin plus intensive diet plus exercise	45	1	2.2	—	—	—	—
	C: intensive diet plus exercise	46	—	—	—	—	—	—
Iqbal Hydrie 2012	I1: metformin plus intensive diet and physical activity	95	5	5.3	—	—	—	—
	C1: intensive diet and physical activity	114	0	0	—	—	—	—
	C2: standard care	108	0	0	—	—	—	—
Liao 2012	I: metformin	51	1	2.0	—	—	—	—
	C: acarbose	50	2	4.0	—	—	—	—

(Continued)

Ji 2011	I1: metformin	52	—	—	—	—	—	—
	C1: Intensive diet plus exercise	60	—	—	—	—	—	—
	C2: standard care	64	—	—	—	—	—	—
Lu 2010	I: metformin	115	21	18.3	—	—	—	—
	C: standard care	111	17	15.3	—	—	—	—
BIGPRO1 2009	I: metformin	21	—	—	—	—	—	—
	C: placebo	36	—	—	—	—	—	—
Chen 2009	I: metformin	44	—	—	—	—	—	—
	C: standard care	46	—	—	—	—	—	—
Jin 2009	I: metformin	45	3	6.7	—	—	—	—
	C1: standard care	41	—	6.7	—	—	—	—
	C2: rosiglitazone	41	3	6.7	—	—	—	—
Li 2009	I: metformin	77	—	—	—	—	—	—
	C: intensive diet plus exercise	83	—	—	—	—	—	—
Wang 2009	I: metformin	30	2	6.7	—	—	—	—
	C: standard care	32	—	—	—	—	—	—
IDPP-1 2006	I1: metformin	128	—	—	—	—	—	—
	I2: metformin plus intensive diet and physical activity	121	—	—	—	—	—	—
	C1: intensive exercise plus diet	120	—	—	—	—	—	—
	C2: standard care	133	—	—	—	—	—	—
Maji 2005	I1: metformin	—	—	—	—	—	—	—

(Continued)

	C1: intensive lifestyle intervention	—	—	—	—	—	—	—
	C2: rosiglitazone	—	—	—	—	—	—	—
	C3: acarbose	—	—	—	—	—	—	—
Fang 2004	I: metformin	44	4	9.1	—	—	—	—
	C1: acarbose	45	5	11.1	—	—	—	—
	C2: intensive exercise and diet	36	0	0	—	—	—	—
	C3: standard care	35	0	0	—	—	—	—
DPP/DPPOS 2002	I: metformin	1073	—	—	—	—	—	—
	C1: intensive exercise and diet	1079	—	—	—	—	—	—
	C2: placebo	1082	—	—	—	—	—	—
Lu 2002	I1: metformin	80	—	—	—	—	—	—
	C1: standard care	75	1	1.3	—	—	—	—
	C2: standard care plus diet instruction every 6th month	64	—	—	—	—	—	—
	C3: standard care plus fibre diet	51	1	2.0	—	—	—	—
Li 1999	I: metformin	33	2	6.1	—	—	—	—
	C: placebo	37	1	2.7	—	—	—	—
Papoz 1978	I1: metformin (plus placebo)	—	—	—	—	—	—	—
	C1: glibenclamide plus placebo	—	—	—	—	—	—	—
	C2: placebo	—	—	—	—	—	—	—

—: denotes not reported

C: comparator; **I**: intervention; **N**: number of participants.

Appendix 13. Adverse events (III)

Trial ID	Intervention(s) and comparator(s)	Participants included in analysis (N)	Participants with a specific adverse event (description)	Participants with at least one specific adverse events (N)	Participants with at least one specific adverse event (%)
Alfawaz 2018	I: metformin	59	—	—	—
	C1: intensive diet plus exercise	73	—	—	—
	C2: standard care	85	—	—	—
PREVENT-DM 2017	I1: metformin	29	(1) gastrointestinal disturbances	(1) 9	(1) 27.6
			(2) dizziness/vertigo	(2) 1	(2) 3.4
			(3) headache	(3) 1	(3) 3.4
			C1: intensive diet plus exercise	33	—
	C2: standard care	30	0	0	0
Zeng 2013	I: metformin	68	—	—	—
	C1: Standard care	66	—	—	—
	C2: pioglitazone	70	—	—	—
Zhao 2013	I: metformin plus intensive diet plus exercise	45	—	—	—
	C: intensive diet plus exercise	46	—	—	—
Iqbal Hydrie 2012	I1: metformin plus intensive diet and physical activity	95	—	—	—
	C1: intensive diet and physical activity	114	—	—	—
	C2: standard care	108	—	—	—
Liao 2012	I: metformin	51	Cerebral haemorrhage	1	2.0
	C: acarbose	50	(1) lung cancer (2) hepatitis	(1) 1 (2) 1	(1) 2.0 (2) 2.0
Ji 2011	I1: metformin	52	—	—	—
	C1: Intensive diet plus exercise	60	—	—	—

(Continued)

	C2: standard care	64	—	—	—
Lu 2010	I: metformin	115	Taste abnormalities 13	13	11.3
	C: standard care	111	Taste abnormalities 1	1	0.9
BIGPRO1 2009	I: metformin	21	—	—	—
	C: placebo	36	—	—	—
Chen 2009	I: metformin	44	—	—	—
	C: standard care	46	—	—	—
Jin 2009	I: metformin	45	Severe gastrointestinal reactions	3	6.7
	C1: standard care	41	—	—	—
	C2: rosiglitazone	41	(1) facial oedema (2) intolerance of both lower limbs	(1) 1 (2) 2	(1) 2.4 (2) 4.9
Li 2009	I: metformin	77	—	—	—
	C: intensive diet plus exercise	83	—	—	—
Wang 2009	I: metformin	30	—	—	—
	C: standard care	32	—	—	—
IDPP-1 2006	I1: metformin	128	(1) Cardiovascular event Only reported for both metformin groups together: (2) Hypoglycaemia (3) Gastrointestinal symptoms (4) CVD	(1) 0 (2) 22 (3) 5 (4) 10	(1) 0 (2) 8.8 (3) 2.0 (4) 4.0
	I2: metformin plus intensive diet and physical activity	121	(1) Cardiovascular event Only reported for both metformin groups together: (2) Hypoglycaemia (3) Gastrointestinal symptoms (4) CVD	(1) 5 (2) 22 (3) 5 (4) 10	(1) 4.1 (2) 8.8 (3) 2.0 (4) 4.0
	C1: intensive exercise plus diet	120	(1) Cardiovascular event (2) Hypoglycaemia (3) Gastrointestinal symptoms (4) CVD	(1) 4 (2) 0 (3) 0 (4) 18	(1) 3.3 (2) 0 (3) 0 (4) 15

(Continued)

	C2: standard care	133	(1) Cardiovascular event (2) Hypoglycaemia (3) Gastrointestinal symptoms (4) CVD	(1) 2 (2) 0 (3) 0 (4) 26	(1) 1.5 (2) 0 (3) 0 (4) 19.5
Maji 2005	I1: metformin	—	—	—	—
	C1: intensive diet plus exercise	—	—	—	—
	C2: rosiglitazone	—	—	—	—
	C3: acarbose	—	—	—	—
Fang 2004	I: metformin	44	(1) Diarrhea (2) Death (liver cancer)	(1) 3 (2) 1	(1) 6.8 (2) 2.3
	C1: acarbose	45	(1) Abdominal distension and diarrhoea (2) Rash (3) Frequent venting	(1) 3 (2) 1 (3) 1	(1) 6.7 (2) 2.2 (3) 2.2
	C2: intensive exercise and diet	36	(1) Gastrointestinal side effects (2) Rashes	(1) 0 (2) 0	(1) 0 (2) 0
	C3: standard care	35	(1) Gastrointestinal side effects (2) Rashes	(1) 0 (2) 0	(1) 0 (2) 0
DPP/DPPOS 2002	I: metformin	1073	—	—	—
	C1: intensive exercise and diet	1079	—	—	—
	C2: placebo	1082	—	—	—
Lu 2002	I1: metformin	80	—	—	—
	C1: standard care	75	Death (cerebral thrombosis with pulmonary infection)	1	1.3
	C2: standard care plus diet instruction every 6th month	64	—	—	—
	C3: standard care plus fibre diet	51	Stomach cancer	1	2.0
Li 1999	I: metformin	33	Mild diarrhoea and nausea	3	9.1
	C: placebo	37	(1) Mild nausea (2) Raised liver enzymes	(1) 6 (2) 1	(1) 16.2 (2) 2.7

(Continued)

Papoz 1978	I1: metformin (plus placebo)	—	—	—	—
	C1: glibenclamide plus placebo	—	—	—	—
	C2: placebo	—	—	—	—

—: denotes not reported

C: comparator; CVD: cardiovascular disease; I: intervention; N: number of participants.

Appendix 14. Survey of authors providing information on included trials

Trial ID	Date trial author contacted	Date trial author replied	Date trial author was asked for additional information (short summary)	Date trial author provided data (short summary)
Alfawaz 2018	7th of April 2019	No reply	NA	NA
PREVENT-DM 2017	11th of August 2017	No reply	Asked if they could provide additional information on the trial	NA
Zeng 2013	No contact information available	NA	NA	NA
Zhao 2013	5th of August 2019	NA	No contact information provided in publication. Hospital was called to get contact information on first author, no one answered the phone	NA
Iqbal Hydrie 2012	9th of August 2017	No reply	Asked if they could provide additional information on the trial including a trial protocol	NA
Liao 2012	5th of August 2019	NA	No contact information provided in publication. Hospital was called to get contact information on first author, no one answered the phone.	NA
Ji 2011	5th of August 2019	No reply.0	Contacted through e-mail	NA
Lu 2010	No contact information available	NA	NA	NA
BIGPRO1 2009	14th of August 2017	14 August 2017	Asked for detailed number of diabetes, deaths, CVD and adverse events.	Primary author provided contact information on the investigator possessing trial data. She was contacted 25 March 2019. No reply was given.

(Continued)

Chen 2009	5th of June 2019	NA	No contact information provided in publication. Hospital was called to get contact information on first author, no one answered the phone.	NA
Jin 2009	No contact information available	NA	NA	NA
Li 2009	5th of June 2019	NA	No contact information provided in publication. Hospital was called to get contact information on first author, colleague refused to forward	NA
Wang 2009	5th of June 2019	NA	No contact information provided in publication. Hospital was called to get contact information on first author, colleague refused to forward	NA
IDPP-1 2006	14th of April 2015	No reply	Asked for change of HbA1c and insulin level	NA
Maji 2005	No contact information available	NA	NA	NA
Fang 2004	14th of April 2015	No reply	Asked for change of HbA1c and insulin level and detailed number of CVD	NA
DPP/DPPOS 2002	20th of December 2014	23 December 2014	Asked for detailed number of diabetes, deaths, CVD and adverse events.	NA
Lu 2002	5th of August 2019	NA	No contact information provided in publication. Hospital was called to get contact information on first author, colleague refused to forward	NA
Li 1999	14th of April 2015	NA	Asked for detailed number of CVD	NA
Papoz 1978	4th of May 2016	No reply	No contact information could be identified for the first author. Contact information on one of the other authors was identified through an Internet search (Dr Eschwege)	NA

CVD: cardiovascular disease; **HbA1c:** glycosylated haemoglobin A1c; **NA:** not applicable.

Appendix 15. Checklist to aid consistency and reproducibility of GRADE assessments: metformin versus placebo or diet and exercise

Items	(1) All-cause mortality	(2) Incidence of type 2 diabetes mellitus	(3) Serious adverse events	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction/stroke	(6) Health-related quality of life	(7) Socio-economic effects	
Trial limitations (risk of bias) ^a	Was random sequence generation used (i.e. no potential for selection bias)?	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes	Yes	Yes	Yes	No (↓)	Yes
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes	Yes	Yes	Yes	No (↓)	Yes
	Was an objective outcome used?	Yes	Yes	Yes	Yes	Yes	No (↓)	Yes
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^e	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Unclear	Unclear	No (↓)	Unclear	Unclear	Unclear	Yes
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the trials end up as scheduled (i.e. not stopped early)?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)	
Inconsistency ^b	Point estimates did not vary widely?	Yes	Yes	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
	To what extent did confidence intervals overlap (substantial: all confidence intervals over-	Substantial	Substantial					

(Continued)

lap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?

Was the direction of effect consistent?	No (↓)	Yes
What was the magnitude of statistical heterogeneity (as measured by I ²) - low (I ² < 40%), moderate (I ² 40% to 60%), high I ² > 60%)?	Low	Moderate
Was the test for heterogeneity statistically significant (P < 0.1)?	Not statistically significant	Statistically significant (↓)

Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Imprecision ^c	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	No (↓)	Yes	Not applicable	Not applicable	Not applicable	N/A	N/A
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)? ^e	High	High				High	High
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)? ^e	Moderate	Large				Small (↓)	Small (↓)

(Continued)

	Was the outcome a common event (e.g. occurs more than 1/100)?	No (↓)	Yes				Not applicable	Not applicable
Publication bias ^d	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	There was no evidence of funnel plot asymmetry?	Not applicable	Unclear	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
	There was no discrepancy in findings between published and unpublished trials?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials

^bQuestions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

^cWhen judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful

^dQuestions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials

^eDepends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation.

Appendix 16. Checklist to aid consistency and reproducibility of GRADE assessments: metformin versus intensive diet plus exercise

Items	(1) All-cause mortality	(2) Incidence of type 2 diabetes mellitus	(3) Serious adverse events	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction/stroke	(6) Health-related quality of life	(7) Socio-economic effects
Trial limitations (risk of bias) ^a	Was random sequence generation used (i.e. no potential for selection bias)?	Unclear	Unclear	Yes	Unclear	Unclear	Not applicable
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes	Yes	Yes	Yes	Yes
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes	Yes	Yes	Yes	Yes
	Was an objective outcome used?	Yes	Yes	Yes	Yes	Yes	Yes
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^e	Yes	Yes	Unclear	Yes	Yes	Yes
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Unclear	Unclear	No (↓)	Unclear	Unclear	Yes
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes	Yes	Yes	Yes	Yes
Did the trials end up as scheduled (i.e. not stopped early)?	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)	No (↓)	
Inconsistency ^b	Point estimates did not vary widely?	Yes	No (↓)	Not applicable	Not applicable	Not applicable	Not applicable
	To what extent did confidence intervals overlap (substantial: all confidence intervals over-	Substantial	Some				

(Continued)

lap at least one of the included studies point estimate;
some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?

Was the direction of effect consistent?	No (↓)	Yes
What was the magnitude of statistical heterogeneity (as measured by I ²) - low (I ² < 40%), moderate (I ² 40% to 60%), high I ² > 60%)?	Low	High (↓)
Was the test for heterogeneity statistically significant (P < 0.1)?	Not statistically significant	Statistically significant (↓)

Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes	Yes	Yes	Yes
Imprecision ^c	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	No (↓)	No (↓)	Not applicable	Not applicable	Not applicable	N/A
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)? ^e	High	High				High
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)? ^e	Small (↓)	Moderate				Small (↓)

(Continued)

	Was the outcome a common event (e.g. occurs more than 1/100)?	No (↓)	Yes					Not applicable
Publication bias ^d	Was a comprehensive search conducted?	Yes	Yes	Yes	Yes	Yes		Yes
	Was grey literature searched?	Yes	Yes	Yes	Yes	Yes		Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes	Yes	Yes		Yes
	There was no industry influence on studies included in the review?	Yes	Yes	Yes	Yes	Yes		Yes
	There was no evidence of funnel plot asymmetry?	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable		Not applicable
	There was no discrepancy in findings between published and unpublished trials?	Unclear	Unclear	Unclear	Unclear	Unclear		Unclear

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials

^bQuestions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

^cWhen judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful

^dQuestions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials

^eDepends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation.

Appendix 17. Checklist to aid consistency and reproducibility of GRADE assessments: metformin versus acarbose

Items	(1) All-cause mortality	(2) Incidence of type 2 diabetes mellitus	(3) Serious adverse events	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction/stroke	(6) Health-related quality of life	(7) Socio-economic effects
Trial limitations (risk of bias) ^a	Was random sequence generation used (i.e. no potential for selection bias)?	Yes	Unclear	Unclear	Not applicable	Not applicable	Not applicable
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear	Unclear			
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes	Yes			
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes	Yes			
	Was an objective outcome used?	Yes	Yes	Yes			
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^e	Yes	Yes	Unclear			
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Unclear	Unclear	No (↓)			
	No other biases reported (i.e. no potential of other bias)?	Yes	Yes	Yes			
	Did the trials end up as scheduled (i.e. not stopped early)?	Yes	Yes	Yes			
Inconsistency ^b	Point estimates did not vary widely?	Not applicable	Yes	Not applicable			
	To what extent did confidence intervals overlap (substantial: all confidence intervals over-		Substantial				

(Continued)

lap at least one of the included studies point estimate;
some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?

Was the direction of effect consistent? Yes

What was the magnitude of statistical heterogeneity (as measured by I^2) - low ($I^2 < 40\%$), moderate ($I^2 40\%$ to 60%), high $I^2 > 60\%$)? Low

Was the test for heterogeneity statistically significant ($P < 0.1$)? Not statistically significant

Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes
Imprecision ^c	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	Not applicable	Yes	Not applicable
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100 to 300 participants, low: < 100 participants)? ^e	Low (↓)	Intermediate	Low (↓)
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)? ^e	Small (↓)	Small (↓)	Small (↓)

(Continued)

	Was the outcome a common event (e.g. occurs more than 1/100)?	No (↓)	Yes	Yes
Publication bias ^d	Was a comprehensive search conducted?	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	No (↓)	No (↓)	No (↓)
	There was no evidence of funnel plot asymmetry?	Not applicable	Not applicable	Not applicable
	There was no discrepancy in findings between published and unpublished trials?	Unclear	Unclear	Unclear

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials

^bQuestions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

^cWhen judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful

^dQuestions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials

^eDepends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation.

Appendix 18. Checklist to aid consistency and reproducibility of GRADE assessments: metformin versus thiazolidinediones

Items	(1) All-cause mortality	(2) Incidence of type 2 diabetes mellitus	(3) Serious adverse events	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction/stroke	(6) Health-related quality of life	(7) Socio-economic effects
Trial limitations (risk of bias) ^a	Was random sequence generation used (i.e. no potential for selection bias)?	Not applicable	Unclear	Unclear	Not applicable	Not applicable	Not applicable
	Was allocation concealment used (i.e. no potential for selection bias)?		Unclear	Unclear			
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?		Yes	Yes			
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?		Yes	Yes			
	Was an objective outcome used?		Yes	Yes			
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^e		Yes	Unclear			
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?		Unclear	No (↓)			
	No other biases reported (i.e. no potential of other bias)?		Unclear	Yes			
	Did the trials end up as scheduled (i.e. not stopped early)?		Yes	Yes			
Inconsistency ^b	Point estimates did not vary widely?		Yes	Not applicable			
	To what extent did confidence intervals overlap (substantial: all confidence intervals over-		Substantial				

(Continued)

	lap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?		
	Was the direction of effect consistent?	Yes	
	What was the magnitude of statistical heterogeneity (as measured by I ²) - low (I ² < 40%), moderate (I ² 40% to 60%), high I ² > 60%)?	Low	
	Was the test for heterogeneity statistically significant (P < 0.1)?	Not statistically significant	
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes
Imprecision ^c	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	Yes	Not applicable
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: <100 participants)? ^e	Intermediate	Low (↓)
	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)? ^e	Small (↓)	Small (↓)

(Continued)

	Was the outcome a common event (e.g. occurs more than 1/100)?	Yes	Yes
Publication bias ^d	Was a comprehensive search conducted?	Yes	Yes
	Was grey literature searched?	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes
	There was no industry influence on studies included in the review?	Unclear	Unclear
	There was no evidence of funnel plot asymmetry?	Not applicable	Not applicable
	There was no discrepancy in findings between published and unpublished trials?	Not applicable	Unclear

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials

^bQuestions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

^cWhen judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful

^dQuestions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials

^eDepends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation

Appendix 19. Checklist to aid consistency and reproducibility of GRADE assessments: metformin plus intensive diet and exercise versus intensive diet and exercise

Items	(1) All-cause mortality	(2) Incidence of type 2 diabetes mellitus	(3) Serious adverse events	(4) Cardiovascular mortality	(5) Non-fatal myocardial infarction/stroke	(6) Health-related quality of life	(7) Socio-economic effects
Trial limitations (risk of bias) ^a	Was random sequence generation used (i.e. no potential for selection bias)?	Unclear	Unclear	Not applicable	Not applicable	Not applicable	Unclear
	Was allocation concealment used (i.e. no potential for selection bias)?	Unclear	Unclear				Unclear
	Was there blinding of participants and personnel (i.e. no potential for performance bias) or outcome not likely to be influenced by lack of blinding?	Yes	Yes				Yes
	Was there blinding of outcome assessment (i.e. no potential for detection bias) or was outcome measurement not likely to be influenced by lack of blinding?	Yes	Yes				Yes
	Was an objective outcome used?	Yes	Yes				Yes
	Were more than 80% of participants enrolled in trials included in the analysis (i.e. no potential reporting bias)? ^e	Yes	Yes				Yes
	Were data reported consistently for the outcome of interest (i.e. no potential selective reporting)?	Yes	Yes				Yes
	No other biases reported (i.e. no potential of other bias)?	Unclear	Unclear				Yes
	Did the trials end up as scheduled (i.e. not stopped early)?	No (↓)	No (↓)				No (↓)
Inconsistency ^b	Point estimates did not vary widely?	Not applicable	No (↓)				Not applicable

(Continued)

	To what extent did confidence intervals overlap (substantial: all confidence intervals overlap at least one of the included studies point estimate; some: confidence intervals overlap but not all overlap at least one point estimate; no: at least one outlier: where the confidence interval of some of the studies do not overlap with those of most included studies)?		Some	
	Was the direction of effect consistent?		No (↓)	
	What was the magnitude of statistical heterogeneity (as measured by I ²) - low (I ² < 40%), moderate (I ² 40% to 60%), high I ² > 60%)?		High (↓)	
	Was the test for heterogeneity statistically significant (P < 0.1)?		Not statistically significant	
Indirectness	Were the populations in included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable
	Were the interventions in the included studies applicable to the decision context?	Highly applicable	Highly applicable	Highly applicable
	Was the included outcome not a surrogate outcome?	Yes	Yes	Yes
	Was the outcome timeframe sufficient?	Sufficient	Sufficient	Sufficient
	Were the conclusions based on direct comparisons?	Yes	Yes	Yes
Imprecision ^c	Was the confidence interval for the pooled estimate not consistent with benefit and harm?	Not applicable	No (↓)	N/A
	What is the magnitude of the median sample size (high: 300 participants, intermediate: 100-300 participants, low: <100 participants)? ^e	Intermediate	Intermediate	High

(Continued)

	What was the magnitude of the number of included studies (large: >10 studies, moderate: 5 to 10 studies, small: < 5 studies)? ^e	Small (↓)	Small (↓)	Small (↓)
	Was the outcome a common event (e.g. occurs more than 1/100)?	No	Yes	Not applicable
Publication bias ^d	Was a comprehensive search conducted?	Yes	Yes	Yes
	Was grey literature searched?	Yes	Yes	Yes
	Were no restrictions applied to study selection on the basis of language?	Yes	Yes	Yes
	There was no industry influence on studies included in the review?	Unclear	Unclear	Yes
	There was no evidence of funnel plot asymmetry?	Not applicable	Not applicable	Not applicable
	There was no discrepancy in findings between published and unpublished trials?	Not applicable	Not applicable	Unclear

^aQuestions on risk of bias are answered in relation to the majority of the aggregated evidence in the meta-analysis rather than to individual trials

^bQuestions on inconsistency are primarily based on visual assessment of forest plots and the statistical quantification of heterogeneity based on I^2

^cWhen judging the width of the confidence interval it is recommended to use a clinical decision threshold to assess whether the imprecision is clinically meaningful

^dQuestions address comprehensiveness of the search strategy, industry influence, funnel plot asymmetry and discrepancies between published and unpublished trials

^eDepends on the context of the systematic review area

(↓): key item for potential downgrading the quality of the evidence (GRADE) as shown in the footnotes of the 'Summary of finding' table(s); **GRADE**: Grading of Recommendations Assessment, Development and Evaluation.

Appendix 20. Health-related quality of life: instruments

Trial ID	Instru- ment	Dimensions (subscales) (no. of items)	Validated instru- ment	Answer options	Scores	Minimum score Maximum score	Weighting of scores	Direction of scales	Minimal important differ- ence
DPP/DP- POS 2002	SF-36 (G)	Physical functioning (PF) (10) Role-physical (RP) (4) Bodily pain (BP) (2) General health (GH) (5) Vitality (VT) (4) Social functioning (SF) (2) Role-emotional (RE) (3) Mental health (MH) (5)	Yes	Lik- ert-scale	Scores for dimensions Physical component summary (PCS) Mental com- ponent summary (MCS)	Minimum scores: 0 Maximum scores:100	No	Higher val- ues mean bet- ter assess- ment	Minimal important differ- ence was defined as HRQoL scores between groups dif- fered by at least 3 %; In other publication (Mar- rero et al) minimal impor- tant difference is defined as two points on either PCS or MCS.

G: generic; **HRQoL:** health-related quality of life; **S:** specific; **SF:** short-form health survey.

CONTRIBUTIONS OF AUTHORS

All review authors read and approved the final review draft.

KM: acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and will be involved in future review updates.

YC: acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review draft and will be involved in future review updates.

MIM: search strategy development and review of drafts.

BR: protocol and review draft, search strategy development, data interpretation and review of drafts.

BH: protocol and review draft, search strategy development, data interpretation and review of drafts.

DECLARATIONS OF INTEREST

Kasper S Madsen (KM): none known

Yuan Chi (YC): none known

Maria-Inti Metzendorf (MM): none known

Bernd Richter (BR): none known

Bianca Hemmingsen (BH): none known

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Internal sources

- West China Hospital of Sichuan University, China.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We changed the definition of the intervention "Metformin monotherapy" in our protocol to "Metformin monotherapy (with or without diet, exercise or both)" because most trials included some element of diet, exercise or both in the intervention groups.

In our protocol, interventions in the control group did not comprise "no antidiabetic treatment". However, we found three trials comparing metformin with this type of intervention after reading all publications. Therefore, we extracted and analysed the data from these trials.

In our protocol we stated that we planned to do subgroup analyses on 'type of comparator (active comparator or placebo/no intervention)'. This subgroup analysis was changed to 'trials designed to blind participants and investigators versus open-labelled trials' to better address issues of risk of bias.

The corresponding author has changed.

NOTES

Portions of the background and methods sections, the appendices, additional tables and figures 1 to 3 of this review are based on a standard template established by Cochrane Metabolic and Endocrine Disorders.

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetes Mellitus, Type 2 [*prevention & control]; Glucose Intolerance; Glycated Hemoglobin A; Hypoglycemic Agents [*therapeutic use]; Metformin [*therapeutic use]; Prediabetic State; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans