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REVIEW ARTICLE

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Metformin for diabetes prevention: update of the evidence base

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ABSTRACT

We have conducted a narrative review based on a structured search strategy, focusing on the effects of metformin on the progression of non-diabetic hyperglycemia to clinical type 2 diabetes mellitus. The principal trials that demonstrated a significantly lower incidence of diabetes in at-risk populations randomized to metformin (mostly with impaired glucose tolerance [IGT]) were published mainly from 1999 to 2012. Metformin reduced the 3-year risk of diabetes by −31% in the randomized phase of the Diabetes Prevention Program (DPP), *vs.* −58% for intensive lifestyle intervention (ILI). Metformin was most effective in younger, heavier subjects. Diminishing but still significant reductions in diabetes risk for subjects originally randomized to these groups were present in the trial's epidemiological follow-up, the DPP Outcomes Study (DPPOS) at 10 years (−18 and −34%, respectively), 15 years (−18 and −27%), and 22 years (−18 and −25%). Long-term weight loss was also seen in both groups, with better maintenance under metformin. Subgroup analyses from the DPP/DPPOS have shed important light on the actions of metformin, including a greater effect in women with prior gestational diabetes, and a reduction in coronary artery calcium in men that might suggest a cardioprotective effect. Improvements in long-term clinical outcomes with metformin in people with non-diabetic hyperglycemia ("prediabetes") have yet to be demonstrated, but cardiovascular and microvascular benefits were seen for those in the DPPOS who did not *vs.* did develop diabetes. Multiple health economic analyses suggest that either metformin or ILI is cost-effective in a community setting. Long-term diabetes prevention with metformin is feasible and is supported in influential guidelines for selected groups of subjects. Future research will demonstrate whether intervention with metformin in people with non-diabetic hyperglycemia will improve long-term clinical outcomes.

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Introduction

A new diagnosis of type 2 diabetes mellitus (henceforth referred to as "type 2 diabetes" for brevity) is life-transforming, requiring a life-long burden of healthcare, the need to understand and accept the associated risks of adverse long-term outcomes, and financial and other consequences[1]. The management of people at risk of developing type 2 diabetes, therefore, needs to be conducted with care, to avoid labeling them with the same kind of issues. Evidence has built in recent years that so-called "prediabetes" (see below for a discussion of the use of this term) is associated with an increased long-term risk of death or cardiovascular disease, compared with people with normal glucose regulation, especially in people who already have atherosclerotic cardiovascular disease (Figure 1)[2,3]. This has led to an increasing interest in earlier intervention in the time course of dysglycemia, focusing on the period before type 2 diabetes is diagnosed.

At the time of writing, metformin has a therapeutic indication for the prevention or delay of a new diagnosis of type 2 diabetes in at-risk subjects in 66 countries[4]. Influential guidelines for the management of dysglycemia or cardiovascular risk now acknowledge a role for metformin for diabetes prevention in defined subgroups of people at risk of developing diabetes due to the presence of prediabetes/non-diabetic hyperglycemia (see Box 1 for diagnostic criteria for the diagnosis of these conditions[5–7]).

Box 1 . Summary of diagnostic criteria for different forms of prediabetes/nondiabetic hyperglycaemia.

	Fasting plasma glucose [mg/dL (mmol/L)]	2-h plasma glucose [mg/dL (mmol/L)]
Normal glucose tolerance (NGT)	<100 (<5.6)	<140 (<7.8)
Impaired fasting glucose (IFG)	100–125 (5.6–6.9)[a]	Non-diabetic: <200 (11.1)
Isolated IFG	100–125 (5.6–6.9)	<140 (<7.8)
Impaired glucose tolerance (IGT)	Non-diabetic: <126 (7.0)	140–199 (7.8–11.0)
Isolated IGT	<100 (<5.6)	140–199 (7.8–11.0)
Combined IFG/IGT	100–125 (5.6–6.9)	140–199 (7.8–11.0)

FPG: fasting plasma glucose; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; NGT: normal glucose tolerance. Adapted from Reference[8] under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/).
[a]The 100 mg/dL/5.6 mmol/L cut-off for IFG applies to guidance from the American Diabetes Association[5] and the European Association for the Study of Diabetes/European Society of Cardiology[6]; the lower cut-off for diagnosing IFG is 110 mg/dL (6.1 mmol/L) according to the World Health Organization[7].

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This article has been corrected with minor formatting changes. These changes do not impact the academic content of the article.

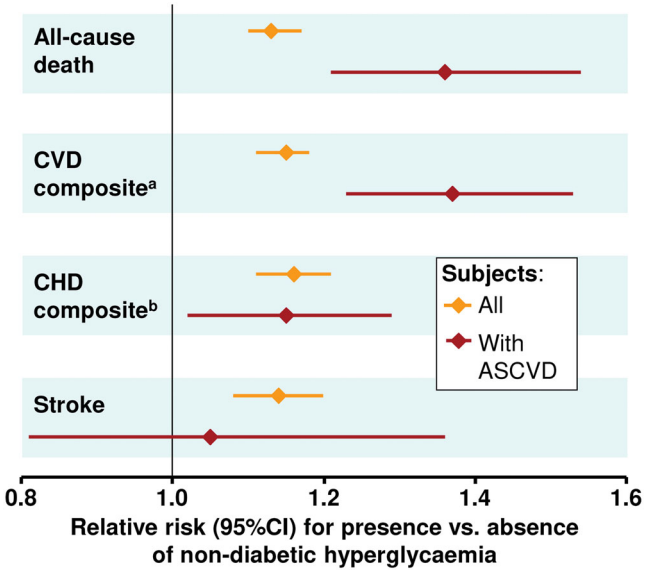

Figure 1. Risks of adverse clinical outcomes associated with non-diabetic hyperglycaemia according to the presence or absence of atherosclerotic cardiovascular disease (ASCVD) from a meta-analysis of 129 studies involving a total of more than 10 million participants. Composites of [a]cardiovascular disease (CVD) and [b]coronary heart disease (CHD) were as reported in individual studies within this meta-analysis. All forms and definitions of non-diabetic hyperglycaemia were included, also as reported in individual studies. Drawn from data presented in reference[2].

We conducted a detailed review of the effects of metformin for diabetes prevention in 2015[8]. Given the continuing expansion in the therapeutic use of metformin for this purpose, we have revisited this area. In the current review, we have summarized the current evidence base for diabetes prevention with metformin, with a focus on new studies and guidelines.

About this review

The main source of literature for this narrative literature review was from a PubMed search for "metformin [ti] AND (*diabetes [ti] OR prediabetes OR non-diabetic hyperglycemia OR 'impaired glucose tolerance' OR IGT OR 'impaired fasting glucose' OR IFG OR 'gestational diabetes') AND (prevention OR delay*)". The 732 search hits (14 May 2021) were examined by eye for articles of interest. The contents of reference lists of selected studies and references provided by authors provided additional material for inclusion. The literature on this subject is large. Accordingly, we have divided our review into two main parts: concise highlights of material included in our previous review published in 2015[8], and a more detailed account of later evidence published since then.

Prior gestational diabetes mellitus (GDM) and polycystic ovary syndrome (PCOS) are also important risk factors for developing clinical (permanent) type 2 diabetes. We have included a brief review of the literature that explored the potential of metformin to prevent diabetes onset in subjects with these conditions. These aspects are dealt with separately to the main subject of prevention or delay of type 2 diabetes. The effects of metformin on glycemia in established GDM, on maternal or fetal pregnancy outcomes, or complications of pregnancy, are beyond the scope of our review and are not discussed here.

The term, "prediabetes" remains widely used, including by the American Diabetes Association (ADA) in its Standards of Care for 2021[9]. This term has attracted controversy, however, partly due to a perception that large numbers of people with "prediabetes" will never develop clinical diabetes, but are nevertheless associated with it, and thus become "medicalized"[10]. The World Health Organization has abandoned the term in favor of "intermediate hyperglycemia"[5]. Nevertheless, much of the relevant literature is based on this term and we have used it in this review to reflect this where unavoidable. Where possible, however, we have used the term, "non-diabetic hyperglycemia".

Randomized diabetes prevention trials with metformin in subjects with impaired glucose tolerance or impaired fasting glucose at baseline

Earlier randomized trials (2015 or earlier)

An overview of earlier evidence relating to diabetes prevention with metformin from randomized trials (including post-randomization epidemiological follow-up) is presented in Table 1. Diabetes prevention with metformin was demonstrated initially in small, randomized, placebo-controlled studies in China that compared the effects of metformin on diabetes incidence with placebo (published in 1999[11] and 2001[12]) in populations with impaired glucose tolerance (IGT). The large ($N = 3234$) Diabetes Prevention Program (DPP) in the USA in subjects with IGT and high-normal fasting plasma glucose (FPG) provided the definitive evidence to support the concept of diabetes prevention with metformin in 2003[14].

Other randomized trials also demonstrated a significant level of diabetes prevention with metformin, including the Indian DPP (subjects with IGT, metformin *vs.* standard lifestyle advice or intensive lifestyle intervention, published in 2006)[33], the CANOE study in Canada (metformin + low-dose thiazolidinedione *vs.* placebo, also published in 2010)[34], and a study in Pakistan (metformin *vs.* standard lifestyle advice, published in 2012)[35], The Early Diabetes Intervention Trial found no significant effect of metformin on diabetes incidence in subjects with IFG and/or IGT.

Subgroup analyses from the diabetes prevention program

Numerous subsidiary publications from the DPP are summarized in Table 1. Metformin improves insulin-stimulated glucose metabolism in subjects with non-diabetic hyperglycaemia[36,37]; this raises the question of whether a short-term pharmacologic reduction in glucose was masking the presence of type 2 diabetes in the metformin group. An analysis from the DPP showed that the reduction in the risk of incident diabetes with metformin changed from 31% (at the end of metformin treatment) to −25% (after 1–2 weeks of washout)[15]. Accordingly, the majority of the effect of metformin on new type 2 diabetes

Table 1. Diabetes prevention with metformin from randomised trials: highlights up to 2015.

Study	Main findings
Li et al.[11]	66% RRR for metformin *vs.* placebo in 70 subjects with IGT
Wenying et al.[12]	RRR for new-onset diabetes *vs.* standard lifestyle advice were −88% for additional metformin; −87% for acarbose, −43% for ILI, in 321 subjects with IGT
EDIT[a,13]	No significant effects on the risk of diabetes *vs.* placebo in subjects with IFG treated with metformin (RRR 0.99, $p = .94$) or metformin + acarbose (RRR 1.02, $p = .91$); similar results were seen in those who also had IGT at baseline (RRR 1.09, $p = .70$ [metformin alone], and RRR 0.72, $p = .27$ [metformin + acarbose]).
Diabetes Prevention Program (DPP)	**Main analysis**
	Relative risk reductions (RRR) of 31% with metformin and 58% with ILI (both *vs.* placebo + standard lifestyle advice) over 3.2 y in a population of 3324 subjects with IGT and high-normal FPG[14]
	NNT to prevent 1 incident case of diabetes was 6.9 (ILI) and 13.9 (metformin)
	Median delay in diabetes onset 3 years for metformin and 11 years for ILI
	Mean weight loss was 5.6 kg (ILI), 3.1 kg (metformin) and 0.1 kg (placebo)
	Metformin was more effective in younger subjects and subjects with higher BMI (similar efficacy for metformin and ILI for those with BMI $\geq$35 kg/m^2 or age $\leq$44 years)
	Later subgroup analyses
	About one quarter of the effect of metformin on the risk of new-onset diabetes was due to a short-lived effect of treatment that reversed on washout[15]
	Metformin (RRR −49 *vs.* −23%) and ILI (RRR −68 *vs.* −47%) were more effective ($p = .03$) in preventing diabetes in subjects who completed college education[16]
	11/19 baseline clinical variables predicted transition to diabetes and 6/19 predicted reversion to NGT[17]
	Larger effect on cardiovascular risk factors (hypertension, dyslipidemia) in the ILI group *vs.* other groups (driven largely by changes in glycemic status)[18,19]
	Metformin and ILI reduced the level of atherogenic small, dense LDL[20]
	The incidence *vs.* placebo of the metabolic syndrome was reduced by −41% on ILI ($p < .001$) and by −17% on metformin ($p = .03$)[19]
	Cardiovascular risk factors deteriorated on progression to diabetes and reverse during reversion to NGT (effects were largest in the ILI group)[21]
	Serum ALT was lower for metformin *vs.* placebo, mostly mediated by weight loss[22]
	Metformin and ILI reduced C-reactive protein and tPA (and to a lesser extent, fibrinogen) *vs.* placebo (effects were larger in the ILI group)[23] – but only in those who did not develop diabetes[24]
	Renal function remained similar in each group[25,26]
	Loss of ovarian function in women (post-menopause or oophorectomy) had no effect on diabetes risk.[27]
	Small increases in HRQoL for ILI only (no effect of metformin or placebo), associated with weight loss and increased physical activity[28]
	Genetic variants associated with a metformin transporter (*SLC47A1*, *SLC22A1*) and components of the AMP kinase system influenced the diabetes prevention response to metformin[29]
	Higher levels of a genetic risk score known to predict lower insulin sensitivity did not alter the improvements in insulin sensitivity seen with metformin or ILI[30]
	Cost/QALY was USD 1100 for ILI and USD 31,300 for metformin (ILI dominated metformin for incremental cost-effectiveness;); health system perspective[31]
	Costs per case of diabetes prevented/delayed were USD 13,200 (ILI) and USD 14,300 (metformin) from a societal perspective[32]
Indian DPP[33]	Similar RRR for new-onset diabetes *vs.* standard lifestyle advice for metformin + standard lifestyle advice (−26%); metformin + ILI (−28%); ILI (−29%) in 531 subjects with IGT
CANOE[34]	RRR for new-onset diabetes *vs.* standard lifestyle advice was −77% for additional twice-daily low-dose metformin (500 mg) + rosiglitazone (2 mg) in 207 subjects with IGT
Iqbal Hydrie et al.[35]	RRR for new-onset diabetes *vs.* standard lifestyle advice was −77% for additional metformin in 317 subjects with IGT

ALT: alanine aminotransferase; FPG: fasting plasma glucose; HRQoL: health-related quality of life; ILI: intensive lifestyle intervention.
Figures in parentheses are 95% confidence intervals. References are as shown or included in reference[8].
[a]Early Diabetes Intervention Trial.

incidence did not appear to have been due to metformin's antihyperglycemic effect masking an underlying diabetic state.

Another important analysis assessed the effects of 19 clinical variables measured at baseline on the likelihood of progressing from IGT to diabetes or reverting to normal glucose tolerance (NGT)[17]. Predictors of a change in glycemic status were generally different for the metformin and ILI groups:

- Age, current smoking, prior diagnosis of PCOS, family history of diabetes, and lower adherence to interventions predicted progression to diabetes in the metformin group only;
- Physical activity >150 min/week predicted progression to diabetes in the ILI group only;
- Higher FPG and higher triglycerides predicted progression to diabetes in both the metformin and ILI groups.

Predictors for regression to NGT were:

- Male gender, a college graduate degree, and lower systolic blood pressure SBP predicted reversion to NGT on metformin only;
- Lower FPG, lower triglycerides, and lower age-predicted reversion to NGT on both ILI and metformin (no baseline parameter predicted reversion to NGT on ILI only).

The effects of metformin on cardiovascular risk factors were modest in the DPP, with larger effects seen in the ILI group[18,19]. Nevertheless, randomization to metformin was associated with a significant reduction in the incidence of the metabolic syndrome during the study (by −17% [$p = .03$], again with a larger effect of ILI [−41% [$p < .001$]])[19]. In general, effects on cardiovascular risk factors were driven

by (especially adverse) changes in glycemic status and triglycerides in this trial[21,38]. Both metformin and ILI reduced the level of atherogenic small, dense LDL and raised LDL, while metformin increased small HDL[20]. Differences in effects on HDL-C according to race have been proposed[39].

Improvements in the metformin group occurred for the non-classical cardiovascular risk factors, alanine aminotransferase (ALT)[22], C-reactive protein (CRP)[23,40], and tPA[23]. The favorable changes in CRP and tPA in the DPP were seen only in subjects who did not develop diabetes[24]. Once again, changes in these risk factors were mainly associated with weight loss. Indices of renal function, and their effects on the risk of diabetes, differed little between groups[25,26]. Finally, age interacted with the effects of study treatments, as described above, but menopausal status in women did not[27]. Reduced body weight and increased physical activity also accounted for an increase in health-related quality of life (HRQoL) in the ILI group[28]. A reduced frequency of stress incontinence due to weight loss provided one striking example of a mechanism of improved HRQoL in the ILI group[41].

The DPP group conducted a detailed analysis of genetic variants that affected study outcomes in the DPP[29]. Reduced risk of diabetes on metformin, but not in other treatment groups, was seen in subjects with *vs.* without the single nucleotide polymorphisms (SNPs) rs2453583 in the *SLC47A1* and rs8065082gene (HRs 0.68 [0.54,0.86] and 0.78 [0.64, 0.96], respectively), and rs315978 in the *LC22A1* gene (HR 0.67 [0.47, 0.96]); both of these genes encode metformin transporters. The presence of rs11086926 in the *ABCC8* gene, which encodes the SUR sulphonylurea receptor (HR 0.79 [0.63, 0.98]) was also associated with a reduced risk of diabetes on metformin. Increased progression to diabetes was associated with SNPs rs11086926 of the *HNF4a* gene (hepatocyte nuclear factor 4a; HR 1.81 [1.35, 2.43]), rs10213440 of the *PPARGC1A* gene (a transcriptional coactivator involved in energy metabolism; HR 1.31 [1.03, 1.66]), rs4424892 of the *MEF2A* gene and rs6666307 of the *MEF2D* gene (both transcriptional regulator involved in the physiological response to exercise; HRs 1.31 [1.14, 1.80], and 2.15 [1.22,3.80], respectively).

Elsewhere, adverse genetic risk scores for diabetes also predicted increased risk of diabetes in the DPP population but did not interact importantly with the effects of individual study treatments[42–44]. A mutation associated previously with an increased antihyperglycemic response to metformin (the rs11212617 polymorphism in the ataxia-telangiectasia-mutated gene giving rise to the C *vs.* A allele) did not affect the ability of metformin to prevent or delay diabetes[45]. A single nucleotide polymorphism known to be associated with obesity (rs2815752 in the *NEGR1* gene) was associated with long-term weight loss with metformin; 15 other SNPs were not[46]. Another study derived a genetic risk score based on 17 mutations known to affect insulin sensitivity: treatment with metformin or ILI improved the insulin sensitivity index irrespective of the level of this score[30].

Finally, health economic analyses confirmed the cost-effectiveness of the interventions in the DPP[31,32].

Later studies

Published studies

The 2-year PRELLIM (Effect of Linagliptin + Metformin *vs.* Metformin Alone in Patients with Prediabetes) trial evaluated the benefits of adding the DPP4 inhibitor, linagliptin (or no additional treatment) to metformin + ILI in a population of 144 subjects with IGT[47]. The risk of developing diabetes was higher in the metformin + ILI group (hazard ratio [HR] 4.0 [1.2, 13.0]) and the likelihood of regressing to normoglycemia was higher in the triple therapy group (HR 3.3 [1.6, 6.8]).

PREVENT-DM was a small ($n = 92$), pragmatic study in obese Latina women with elevated, but non-diabetic, HbA1c in an urban setting in the USA[48]. Subjects were randomized to receive ILI (based on the DPP and promoted by community health workers), metformin 850 mg BID, or continued usual care for one year. Mean weight loss was larger for ILI (−4.0 kg) than for metformin (−1.1 kg). No data on diabetes prevention *per se* were available from this small study, but its importance lies in its demonstration of delivery of diabetes prevention interventions in a challenging setting.

Studies in progress

A 2-year study in China is randomizing subjects with "impaired glucose regulation" (WHO 1999 diagnostic criteria) to a lifestyle intervention with or without additional metformin 850 mg BID for at least 2 years. Its primary endpoint will be the incidence of diabetes[49]. The Transdiab study will evaluate the efficacy of metformin *vs.* placebo for reducing the risk of post-renal transplant diabetes, a common complication of this procedure[50,51]. A cluster-randomized trial is in progress in Mexico to evaluate the cost-effectiveness of intervention with ILI with or without metformin for 3060 obese subjects with IGT[52]. The primary endpoint will be the incidence of type 2 diabetes.

Other trials, described but yet to report, continue the shift away from the primary measurement of incident diabetes to other endpoints, including clinical outcomes, as summarized below.

Clinical cardiovascular outcomes: **GLINT** (Glucose Lowering In Non-diabetic hyperglycemia Trial) was conceived as a clinical outcomes study of metformin XR (up to 1500 mg/day) *vs.* placebo in people with non-diabetic hyperglycemia and risk factors for cardiovascular disease[53]. It is currently unclear if and when the main part of this study will proceed, due to serious problems relating to the recruitment of subjects, a high level of treatment discontinuation, and funding issues[53]. The **VA-IMPACT** (Investigation of Metformin in Pre-Diabetes on Atherosclerotic Cardiovascular OuTcomes) study is currently recruiting a population of about 8000 people with any form of non-diabetic hyperglycemia at elevated cardiovascular risk for randomization to metformin XR or placebo (NCT02915198). The primary endpoint is a composite of cardiovascular events.

Additional trials being planned or in progress in populations with non-diabetic hyperglycemia will not evaluate the incidence of diabetes as their primary endpoint:

Personalized *vs.* general calorie-restricted diet + metformin: The Personalized Medicine in Pre-diabetes-Towards Preventing Diabetes in Individuals at Risk (PREDICT) study will randomize antihyperglycemic agent-naïve subjects with non-diabetic hyperglycemia to 6 months of either a personalized diet or a more general calorie-restricted diet, each in addition to metformin XR 1500 mg/day[54]. The primary endpoint changes in HbA1c.

Heart failure (HF) outcomes: Strong pathogenetic links have been revealed between diabetes and HF in recent years[55]. The DAN-HEART study is including people with comorbid HF and clinical diabetes or non-diabetic hyperglycaemia[56]. The main outcome will be the incidence of cardiovascular events.

Frailty: Metformin has been shown to improve non-classical cardiovascular risk factors that are also risk factors for developing frailty in later life[57–59]; conversely, frailty is a strong predictor of adverse outcomes in people with diabetes[60]. A 2-year study is randomizing older (≥65 years), non-frail adults with non-diabetic hyperglycemia to metformin or placebo to determine whether metformin can reduce the incidence of frailty[6].

Observational data on diabetes prevention with metformin in subjects with IGT and/or IFG at baseline

The diabetes prevention program outcomes study

Principal analyses released to date

Long-term epidemiologic follow-up of the population of the DPP has been conducted since the end of randomized treatment, in the 88% of the DPP population who entered the DPP Outcomes Study (DPPOS)[61]. All participants who were receiving metformin in the randomized phase who were eligible to continue receiving this treatment according to current guidelines, and who did not require changes to treatment according to their usual care physicians, were offered continued treatment with metformin 850 mg BID. All participants additionally received group-based lifestyle intervention, with subjects previously randomized to ILI receiving additional lifestyle support. The DPPOS Investigators did not provide recommendations on the use of metformin in the prior ILI group. Treatment with a placebo was discontinued.

A significant level of diabetes prevention was still evident in the metformin and lifestyle groups after 10 years of overall follow-up (3 years of randomized treatment + 7 years of epidemiological follow-up (Table 1)[62,63]. The overall incidence of type 2 diabetes/100 person-years during the full ten years of analysis was lowest in the prior ILI group (5.3 [4.8, 5.8]) than in the prior metformin group (6.4 [5.9, 7.1]) or the prior placebo group (7.8 [7.2, 8.6]). However, the incidence rate during the post-randomization (DPPOS) phase was higher for prior ILI (5.9 [5.1, 6.8]) than for prior metformin (4.9 [4.2, 5.7]). This anomalous finding was attributed to a depletion of genetically susceptible individuals in the prior metformin group (some of these had already developed diabetes before the DPPOS phase) and to a 1 kg average weight gain in the ILI group (weight loss was maintained in the prior metformin group)[64].

Data on 15 years of total follow-up for the DPPOS have been published[65], but data for 22 years of total follow-up have only been presented in a symposium at the 2020 congress of the American Diabetes Association (Table 2)[66]: these data remain unpublished and can be described in general terms only at this time[67,68]. Diabetes prevention was still evident at average follow-up duration of 15 years and 22 years. Compared with the prior placebo group, reductions in diabetes incidence for prior metformin were −18% at both time points, and for prior ILI were −27 and −25%. Long-term diabetes prevention is therefore feasible with either intervention, and their efficacy appears to have converged to some extent over time. Figure 2 summarizes the effects of metformin or ILI on diabetes risk at all time points in the DPP or DPPOS.

There were no significant microvascular or macrovascular benefits at 22 years associated with either intervention (as seen elsewhere with ILI after 30 years of follow-up of the DaQing diabetes prevention trial[69]). However, prevention of diabetes *per se* was associated with a lower incidence of major adverse cardiovascular endpoints (−39%), eye disease (−57%), and kidney disease (−37%). There was also a trend towards fewer strokes in the prior metformin group, and a trend for fewer cardiovascular events in those who started metformin before age 45 years, although there were too few events for a definitive analysis. The incidence of nephropathy

Table 2. Overview of findings relating to diabetes prevention from the DPP outcomes study (DPPOS).

Analysis	Overview of main findings
10 years of follow-up[62,63]	Diabetes incidence rates/100,000 person-years were 4.9 (4.2, 5.7) for prior metformin, 5.9 (5.1, 6.8) for prior ILI, and 5.6 (4.8, 6.5) for placebo Overall RRR for incident diabetes were 18% (7, 28) for prior metformin and 34% (24, 42) for prior ILI Weight loss on metformin was maintained during the DPPOS at 10 y (the prior ILI group gained an average of 1 kg) Metformin and ILI were cost saving and increased QALYs *vs.* placebo; overall discounted incremental cost-effectiveness ratio was USD 13,420 for ILI *vs.* metformin[74]
15 years of follow-up[66–68]	Significant diabetes prevention still present for the prior ILI group (RRR −27%) and the prior metformin group (RRR −18%) No microvascular or macrovascular outcomes benefit for either active treatment – however, there were significant cardiovascular and microvascular benefits for subjects who did not *vs.* did develop diabetes from the whole population
22 years of follow-up[66–68]	Significant diabetes prevention still present for the prior ILI group (RRR −25%) and the prior metformin group (RRR −18%) No microvascular or macrovascular outcomes benefit for either active treatment – however, there were significant cardiovascular (RRR −39% for MACE) and microvascular benefits (RRR −57% for eye disease and −37% for kidney disease) for subjects who did not *vs.* did develop diabetes from the whole population

ILI: intensive lifestyle intervention; MACE: major adverse cardiovascular events; RRR: relative risk reduction.
Total follow-up is randomized + observational follow-up. References to "prior ILI" or "prior metformin" groups refer to subjects previously randomised to those groups as no attempt was made to maintain randomised treatment during the DPPOS. Figures in parentheses (X, Y) are 95% confidence intervals.

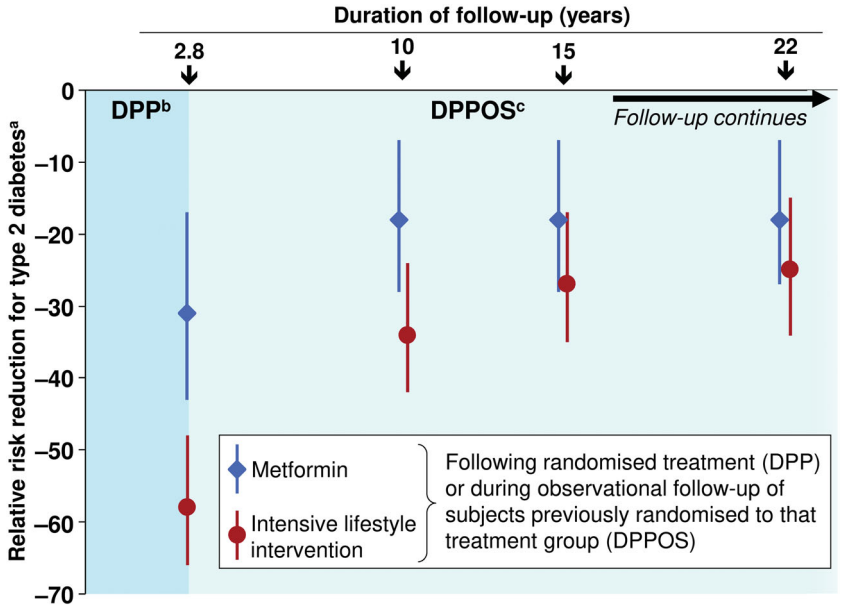

Figure 2. Summary of relative risk reductions for type 2 diabetes in the Diabetes Prevention Program (DPP) and its epidemiological follow-up study, the Diabetes Prevention Program Outcomes Study (DPPOS). [a]Relative to placebo (DPP) or subjects formerly randomised to placebo (DPPOS). [b]Randomized phase. [c]Epidemiologic follow-up. Bars are 95%CI. Points and bars have been displaced laterally where they overlap to improve clarity (all pairs of measurements were from the same time points). Compiled from data presented in references[14,62,65–68].

(albumin: creatinine ratio ≥30 mg/kg) was higher at 20 years follow-up in subjects aged ≥60 years in the prior metformin group (~0.3%), compared with the other prior treatment groups (each ~0.2%)[67]. The significance of this finding is uncertain, as the magnitude of the difference was small, and these data have only been presented in a symposium at the time of writing, and peer-reviewed publication is awaited[67].

Further analyses from the DPPOS

Additional important studies from the DPPOS population are summarized below and in Table 3 [72–77]. Analysis at 15 years total follow-up showed that metformin was more effective in preventing diabetes in women with prior GDM (see below for a more detailed description of effects in this population) and subjects with higher severity of non-diabetic hyperglycemia at baseline[70]. Metformin reduced the risk of diabetes by 17% (based on measurement of FPG) or by −39% (based on measurement of HbA1c) in this study[70].

Weight loss was an important determinant of diabetes prevention in the DPP/DPPOS, as described above. Average weight loss was greater for ILI than the other groups during the randomized phase of the DPP, but maintenance of long-term weight loss from years 6–15 was greatest for metformin[70]. Greater weight loss in year 1 (all groups), older age + continued metformin use (metformin group), and older age and no diabetes or family history of diabetes (ILI group) predicted long-term weight loss on active treatments. Subjects with higher physical activity before the DPP randomization had a greater risk of diabetes: this apparent paradox is explained by the observation that these subjects demonstrated less increase in activity and less weight loss than other subjects during the randomized phase of the trial. Weight loss in the DPP/DPPOS correlated with adherence to metformin[71].

Elevated coronary artery calcium (CAC; measured using a CT scanning technique) is a predictor of increased cardiovascular risk that is used widely in clinical cardiovascular risk assessment[72]. A study at 10 years of DPPOS follow-up (14 years on average in all) found a reduced level of CAC scoring (based on the severity of elevation, or on whether or not elevated CAC was present) in men in the prior metformin group, but not in other treatment groups, or women[73]. The effect in men was independent of other clinical variables or receipt of statin treatment and was hypothesized to represent a potential cardioprotective effect of metformin in men with non-diabetic hyperglycemia. Other evidence of a potential cardioprotective effect of metformin in people with non-diabetic hyperglycemia is available: for example, a prospective observational study reported improved coronary artery endothelial function in people with non-diabetic hyperglycemia (ADA criteria) who did *vs.* did not receive metformin as part of their usual care[74].

In another analysis, neither metformin nor ILI influenced measures of cognition in the DPP/DPPOS[75].

Other observational data

The Carmos study involved an observational comparison of metformin ($n = 95$) or no additional treatment ($n = 271$) in a population of overweight or obese subjects free of diabetes or cardiovascular disease at baseline[76]. Additional metformin treatment reduced the incidence of diabetes in the overall population (risk difference −7% [−13, −1], $p = .012$), with a larger effect in subjects with "prediabetes" (undefined; risk difference −19% [−33, −4], $p = .010$). Treatment with metformin also reduced the risk of developing metabolic syndrome (risk difference −13% [−25, −1], $p = .040$), mainly due to increased HDL-C and reduced plasma glucose.

An uncontrolled, 12-week observational study conducted in Poland and Hungary showed that 3 months of treatment

Table 3. Further published analyses from the DPP outcomes study (DPPOS).

Topic (follow up)	Overview of main findings
Efficacy in subgroups (15 years)[70]	Metformin was more effective in women with *vs.* without prior GDM (rate difference [RD] − 6.6 diabetes cases/100-PY, $p = .01$) and in subjects with higher baseline FPG (RD −3.5 cases/100 PY for FPG ≥ 110 mg/dL (6.1 mmol/L) or HbA1c (RD −3.9 cases/100 PY for baseline HbA1c 6.0–6.4%, $p = .0001$)
Long-term weight loss (15 years)[111]	At 1 year, 29% (metformin) 63% (ILI) and 13% (placebo) had lost ≥ 5% initial body weight, but maintained weight loss for years 6–15 was greater for metformin (6.2% [5.2, 7.2]) *vs.* ILI (3.7% [3.1, 4.4]) or placebo (2.8% [1.3, 4.4]) in the placebo; weight loss in year 1
Coronary calcium (14 years)[73]	Less coronary artery calcium (CAC; measured as severity or presence *vs.* absence on imaging) was present in men (age-adjusted mean CAC severity: 39.5 *vs.* 66.9 Agatston units, $p = .04$; CAC presence: 75 *vs.* 84%, $p = .02$); no effect in women was seen and the effect in men was independent of diabetes, demographic, anthropometric, or metabolic factors, or receipt of statin treatment
Frailty (14 years)[112]	Being in the prior ILI group was associated at year 10 of follow-up with a reduced risk of frailty compared with metformin (OR 0.63 [0.42, 0.94], $p = .022$) or prior placebo (OR 0.62 [0.42, 0.93], $p = .022$; the risk of frailty in the prior metformin did not differ from that for prior placebo (OR 0.99 [0.69. 1.42], $p = .976$)
Cognition (14 years)[75]	Exposure to neither ILI nor to metformin predicted changes in cognition; higher HbA1c predicted impaired cognition, but presence *vs.* absence of type 2 diabetes did not
Malignancy[113]	Randomization to neither metformin nor ILI affected the incidence of cancer significantly during follow-up in the DPPOS.

FPG: fasting plasma glucose; ILI: intensive lifestyle intervention; PY: person-years; RRR: relative risk reduction.
Total follow-up is randomized + observational follow-up. References to "prior ILI" or "prior metformin" groups refer to subjects previously randomised to those groups as no attempt was made to maintain randomised treatment during the DPPOS. Figures in parentheses (X, Y) are 95% confidence intervals.

with metformin XR, administered according to usual care conditions under the care of subjects' physicians to 686 subjects with non-diabetic hyperglycemia based on measurements of FPG or HbA1c[36]. There was no formal diagnosis of diabetes included within the study, but 43% of subjects had their FPG reduced to below the 5.7 mmol/L cut-off used commonly for the diagnosis of IFG (Box 1). Data from 123 subjects with IFG, IGT, or both showed that intervention with ILI, ILI + metformin or ILI + DPP4 inhibitor reduced weight, fasting and post-load glycemia and triglycerides[77].

Diabetes prevention with metformin in other states characterized by insulin resistance

Gestational diabetes

A pregnancy complicated by GDM increases the 10-year risk of future type 2 diabetes substantially[78]. For example, the risk of developing type 2 diabetes was 48% higher over 10 years for women with *vs.* without prior GDM in the placebo group of the DPPOS[79]. Women with a history of GDM in the prior metformin and prior ILI groups in the DPPOS were at lower risk of subsequent development of T2D (relative risk reduction [RRR] − 40 and −35%, respectively, *vs.* women in the prior placebo group[79]. ILI was also effective in preventing diabetes in the subgroup without prior GDM (RRR −30%), although metformin was not. These long-term effects were comparable to those seen in the earlier, randomized phase of the trial[80]. A feasibility trial is underway to support a future placebo-controlled trial that will evaluate the effects of metformin *vs.* placebo on health outcomes (including incident diabetes) in women with GDM[81].

Polycystic ovary syndrome

PCOS is an insulin-resistant state that is the most common cause of anovulatory infertility[82]. Treatment with metformin has been shown to ameliorate the dysglycemia, overweight, and hyperandrogenism that characterizes PCOS, and guidelines recommend a second-line role for metformin in improving fertility in this population[83,84]. Information is lacking on whether metformin can prevent the onset of T2D in women with PCOS[85]. Several observational studies suggested a significant effect of metformin in reducing the risk of future GDM in women with PCOS; meta-analyses of randomized trials do not support such an effect, however[86,87].

Who should receive metformin for diabetes prevention?

Current guidelines

Internationally-influential guidance from Europe (jointly from the European Society of Cardiology [ESC] and the European Association of the Study of Diabetes [EASD])[6], the ADA[9], and the UK National Institute for Health and Care Excellence (NICE)[88] stress lifestyle intervention as the initial intervention to reduce the excess risk of incident diabetes. This is consistent with the well-known association between increased risk of T2D and overweight or obesity and physical inactivity, as described above. All people at risk of (or with) type 2 diabetes who can adopt an intensive lifestyle intervention should do so throughout life.

The ADA and NICE guidelines support the therapeutic use of metformin for diabetes prevention in defined circumstances, while the ESC/EASD guideline provides no recommendation on the pharmacologic management of non-diabetic hyperglycemia (Table 4). Recommendations on the use of metformin generally reflect the findings of the DPP, favoring the use of metformin alongside lifestyle change for younger subjects with higher levels of BMI. Long-term safety monitoring is highlighted including the importance of periodic checks of vitamin B_{12} and renal function (to ensure that patients have not developed a renal contraindication to metformin). The NICE guidance notes additionally that the evidence base for diabetes prevention has been gained with the immediate-release formulation, but that prolonged/extended-release formulation of metformin is now indicated for the prevention or delay of diabetes and may be useful for people who cannot tolerate immediate-release metformin.

Numerous national and regional guidelines on the use of metformin for + diabetes prevention have been developed and are reviewed elsewhere[8]. Most contained

Table 4. Overview of recommendations relating to the use of metformin for the prevention or delay of type 2 diabetes from selected guidelines with international influence.

Sponsor (year)	Summary of recommendation relating to metformin
ADA[9]	Consider adding metformin to lifestyle intervention especially for those with BMI $\geq$35 kg/m^2, those aged $<$60 years, and women with prior GDM
	Monitor vitamin B_{12} periodically, especially where anemia or peripheral neuropathy is present
ESC/EASD[6]	This guideline includes recommendations on lifestyle changes to reduce the risk of new-onset diabetes and cardiovascular risk in subjects with "prediabetes" or diabetes, but does not include any recommendations on interventions on pharmacological intervention in people with non-diabetic hyperglycemia new-onset type 2 diabetes in people with non-diabetic hyperglycaemia
NICE[87]	Use clinical judgement on whether to add metformin to (continued support for) lifestyle intervention for people whose HbA1c is rising despite an attempt at a lifestyle intervention, or for people who are unable to undertake one
	Consider metformin in these situations especially if BMI is $\geq$35 kg/m^2
	Discuss potential risks and benefits carefully, including the potentially lifelong nature of treatment
	Try metformin for 6–12 months and discontinue if there is no improvement in glycaemia
	Monitor renal function initially and periodically (at least twice/per year)

ADA: American Diabetes Association; BMI: body mass index; EASD: European Association of the Study of Diabetes; ESC: European Society of Cardiology; NICE: National Institute for Health and Care Excellence (UK).
All guidelines stress the importance of lifestyle change as the first-line approach to diabetes prevention (see text), and this should be continued during treatment with metformin where possible. Guidance has been paraphrased for conciseness here and readers should always consult the full guidance.

recommendations on the use of metformin consistent with those of the ADA and NICE, as summarized in Table 4.

Is metformin underused in populations with non-diabetic hyperglycemia?

Studies to date suggest that only a small proportion of people with non-diabetic hyperglycemia receive metformin for this condition. For example, a study from the USA reported that the prevalence of self-reported "prediabetes" increased from 5.1% in 2005–2006 to 7.4% in 2013–2014, with a corresponding increase in the use of metformin from 2.4 to 8.3% over this period[89]. Also in the USA, only 0.7% of adults with "prediabetes" were reported to receive metformin between 2005 and 2012[90]. Only 1.9% of people with prediabetes and BMI $\geq$35 kg/m^2, a subgroup with strong support for metformin use in guidelines (see above) were reported to have received metformin in this study. Similarly, a third US study found that only 8.1% of a population of younger people (age $<$60 years) with non-diabetic hyperglycemia (HbA1c 5.7–6.4%) at high risk of diabetes through prior GDM and BMI $\geq$35 kg/m^2 received metformin[91].

The cluster-randomized Prediabetes Informed Decisions and Education (PRIDE) study explored the outcomes of shared decision-making on treatment options among a population of 515 subjects who were about to undertake a diabetes prevention intervention[92]. Pharmacists discussed the contents of evidence-based clinical decision aids for the principal approaches to diabetes prevention. Most subjects opted for ILI (55%), compared with metformin (9%), or both (15%), while 26% declined both. Women and older patients were more likely to choose ILI while increasing BMI predicted higher take-up of both ILI and metformin. Metformin appears to be underused among the population of subjects eligible for it.

Other issues relating to the therapeutic use of metformin for diabetes prevention

Adherence

The majority of the insulin-secreting capacity from pancreatic β-cells has already been lost by the time prediabetic dysglycemia becomes apparent[93], and metformin does not alter the continuing rate of loss of β-cells as clinical diabetes subsequently becomes established[94]. Accordingly, the pharmacologic treatment of prediabetes will be for life and its success will depend on adequate adherence of people with prediabetes to the treatment regimen. Experience from populations with type 2 diabetes shows that periods of non-use of metformin are common during long-term treatment[95]. The DPPOS reported recently that about one-quarter of subjects eligible for metformin did not take it, and that 478/868 subjects reported problems with adherence to metformin over an 11-year period[96]. Higher depression scores, Black ethnicity, and lower initial adherence in the randomized phase of the DPP were among the factors associated with poorer adherence. Strategies to optimize adherence to metformin will be needed, especially given the asymptomatic nature of non-diabetic hyperglycaemia[97]. Some trials in progress in populations with non-diabetic hyperglycemia, described above, are using the XR formulation of metformin, which may support better adherence to therapy than the immediate-release formulation, based on clinical experience in people with type 2 diabetes[98].

Tolerability and safety

The main side-effect of metformin seen in people with type 2 diabetes, i.e. gastrointestinal upsets, such as diarrhea, abdominal pain, and nausea/vomiting, were apparent in the DPP/DPPOS[71] and other randomized trials listed in Table 1; these can be minimized by careful initial dose titration, a (usually temporary) dose reduction where necessary, or use of an extended-release formulation[99,100]. No significant safety issues were observed in the randomized phase of the DPP, and during 7–8 years of follow-up thereafter in the DPPOS[71]. Twenty-two cases of hypoglycemia were reported among the 531 participants in the IDDP[33], a side-effect not usually associated appreciably with metformin in populations with type 2 diabetes. Careful titration from a low starting dose may be useful in non-diabetic subjects, to limit the incidence of side-effects[99].

Lactic acidosis is an extremely rare complication of the treatment of type 2 diabetes with metformin, and the contraindications of this agent are designed to avoid its use during the settings of severe renal impairment and hypoperfusion/hypoxia that might predispose to metformin-associated lactic acidosis[56]. The prevalence of these conditions in subjects with non-diabetic hyperglycemia has not been investigated to our knowledge, but it is likely to be lower than in people with type 2 diabetes of long duration who may be receiving metformin and who may be at risk of developing potential contraindications to metformin, such as severe chronic kidney disease or severe acute HF, etc.

Reduced levels of vitamin B_{12} is a well-known side-effect of metformin treatment during treatment for type 2 diabetes[101] and has been observed in the DPPOS[102]. The authors recommended period screening and B_{12} supplementation, where required, during treatment with metformin.

Metformin has been in continuous clinical use for more than six decades in the management of type 2 diabetes, and its tolerability and safety profiles are well-understood[103]. There is no evidence to suggest that the long-term safety of metformin differs according to the severity of dysglycemia. It is reasonable to assume that the well-established safety and tolerability profiles of metformin observed in people with diabetes will likely apply to people taking metformin to prevent or delay type 2 diabetes, at least until further evidence accumulates relating to the therapeutic profile of metformin specifically in people with non-diabetic hyperglycemia.

Health economics

Numerous reports, reviewed elsewhere[8], have concluded that metformin and ILI based on the DPP are effective and cost-effective approaches to reducing the risk of diabetes in people with non-diabetic hyperglycemia. A systematic review published in 2017 calculated that median incremental cost-effectiveness ratios [ICER] were GBP 7490/quality-adjusted life-year (QALY) for ILI and GBP 8428/QALY for metformin; however, variations between studies in their populations, definitions of non-diabetic hyperglycemia, the nature of the interventions and assumptions used in constructing health economic models contribute to considerable variations in the results of individual studies[104].

Some studies adapted the DPP-based ILI for delivery within a community setting. The PREVENT-DM study, described above, is an interesting example of this approach, in its use of community health workers ("promotoras") to support people with the study interventions in its urban environment[48], as maintaining adherence to a lifestyle change is central to optimizing the benefits from it[105]. The use of "Diabetes Prevention Mentors" did not enhance the effectiveness of a community-based diabetes prevention initiative in the UK, however[106]. The nature of a lifestyle intervention is critical to its effectiveness and cost-effectiveness, however. A recent report from the UK found that low-impact lifestyle intervention was highly cost-effective compared with no intervention, at an incremental cost-effectiveness ratio [ICER] of GBP 44/quality-adjusted life-year (QALY), but would deliver only a 7% reduction in diabetes incidence over 10 years[107]. Metformin was cost-effective at an ICER of GBP 372–5224/QALY, and ILI at an ICER of GBP 2775–7376/QALY, depending on whether diabetes was diagnosed using plasma glucose, OGTT glucose, or HbA1c; metformin was cost-effective compared with either lifestyle intervention when HbA1c was used for diagnosing diabetes. The cost itself is a factor, irrespective of cost-effectiveness. For example, a recent report from Singapore concluded that ICERs of USD 36,663 for ILI (based on the DPP and adapted to local conditions) or metformin (USD 6367) was cost-effective from a societal perspective[108]. However, the authors concluded that the ILI would need to be delivered at a lower cost to be feasible for use as a strategy for diabetes prevention in Singapore.

Summary and conclusions

The potential of metformin to delay or prevent new-onset type 2 diabetes in people with IGT is proven beyond doubt by multiple randomized, controlled trials. Intensive lifestyle intervention was more effective than metformin in preventing diabetes in the DPP and elsewhere, although the efficacy of these interventions was similar in the lowest age category and highest BMI category in the main analysis of the randomized phase of the DPP[14]. Accordingly, lifelong support for an improved lifestyle should be offered to all at risk of diabetes, but guidelines support a role for metformin in people for whom lifestyle intervention is ineffective or impractical, especially where obesity is severe[8]. Physicians and people with non-diabetic hyperglycemia need to make individualized and shared decisions on whether treatment with metformin is appropriate for that individual.

Importantly, clinically and statistically significant levels of diabetes prevention were present two decades after the cessation of randomized treatment in the DPP/DPPOS, for people initially randomized to either ILI or metformin, relative to those initially randomized to placebo. The RRR for diabetes in the prior metformin group remained the same at 10, 15, and 22 years of follow-up at −18% (Table 2, Figure 2). These findings were especially notable as there was no effort to maintain DPP-randomized treatments during the DPPOS (although eligible patients in the metformin group were offered continued treatment). These data attest to the feasibility of long-term diabetes prevention with metformin.

Important research questions remain. We have yet to see improved clinical cardiovascular or microvascular outcomes in members of either the prior ILI or prior metformin groups from the DPPOS, or elsewhere. The observation from 22 years of follow-up that prevention/delay of diabetes *per se* in these groups combined was associated with significant outcomes benefits was encouraging. Further follow-up and more clinical events will be required to establish whether the cardiovascular benefits observed in people with type 2 diabetes randomized to metformin in the UK Prospective Diabetes study will be observed in the DPPOS population previously randomized to metformin[94].

Further data to support a precision medicine approach for targeting the most appropriate subjects to receive metformin

will also be useful. We know that weight loss is a crucial part of any intervention for diabetes prevention, and this has been observed with metformin in the DPP and elsewhere, as described above The observation in the DPP that women with GDM benefitted especially from treatment with metformin (and that women without prior GDM did not)[78] requires further study. The potential for metformin to prevent/delay diabetes in other populations, such as those with PCOS[85], or perhaps antidepressant-induced weight gain and dysglycaemia[109], may be of interest in the future. Further study of populations with isolated IFG would be of interest, as metformin has not yet been clearly shown to reduce the incidence of diabetes in this population[13], but metformin was more effective in subjects with IGT with higher *vs.* lower FPG in the DPP[14,110]. Finally, diabetes prevention studies have used varying dosing schedules for metformin, and the optimal dose of metformin for this purpose has yet to be defined.

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