Metformin and health outcomes: an umbrella review of systematic reviews with meta-analyses

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ABSTRACT

Background: The objective was to capture the breadth of outcomes that have been associated with metformin use and to systematically assess the quality, strength and credibility of these associations using the umbrella review methodology.

Methods: Four major databases were searched until 31 May 2020. Meta-analyses of observational studies and meta-analyses of randomised controlled trials (RCTs) (including active and placebo control arms) were included.

Results: From 175 eligible publications, we identified 427 different meta-analyses, including 167 meta-analyses of observational studies, 147 meta-analyses of RCTs for metformin vs. placebo/no treatment and 113 meta-analyses of RCTs for metformin vs. active medications. There was no association classified as convincing or highly suggestive from meta-analyses of observational studies, but some suggestive/weak associations of metformin use with a lower mortality risk of CVD and cancer. In meta-analyses of RCTs, metformin was associated with a lower incidence of diabetes in people with pre-diabetes or no diabetes at baseline; lower ovarian hyperstimulation syndrome incidence (in women in controlled ovarian stimulation); higher success for clinical pregnancy rate in Poly-Cystic Ovary Syndrome (PCOS); significant reduction in body mass index in people with type 1 diabetes mellitus, in women who have obesity/overweight with PCOS and in obese/overweight women. Of 175 publications, 166 scored as low or critically low quality per AMSTAR 2 criteria.

Conclusions: Observational evidence on metformin seems largely unreliable. Randomized evidence shows benefits for preventing diabetes and in some gynecological and obstetrical settings. However, almost all meta-analyses are of low or critically low quality according to AMSTAR 2 criteria.

Keywords: metformin; umbrella; meta-analysis; GRADE.

Introduction

Metformin (N, N-dimethylbiguanide) belongs to the biguanide class of antidiabetic drugs (containing two linked guanidine rings). The main target tissue of metformin is the liver and its major effect is decreasing hepatic glucose output, largely due to the suppression of gluconeogenesis, which leads to lower fasting blood glucose levels without insulin stimulation and weight gain.([1](#))

Metformin is recommended as first-line pharmacological therapy in patients diagnosed with type 2 diabetes mellitus (T2DM).([2](#)) It has been used widely in the treatment of T2DM for over 50 years and is considered to be quite safe and effective both as monotherapy and in combination with other oral antidiabetic agents and insulin.([3](#)) Besides its use in T2DM and its glucose-lowering effects, there is interest in the use of metformin for the treatment of other conditions, such as polycystic ovary syndrome, diabetic nephropathy and gestational diabetes.([3](#)) Moreover, some observational studies indicated that metformin use in T2DM is associated with a lower risk of overall cancer.([4](#)) Finally, other studies have proposed that metformin can even prolong life and lead to weight loss in obese non-diabetic patients. ([5](#), [6](#))

To the best of our knowledge, no attempt has been performed to systematically assess the quality and the strength of the evidence of systematic reviews with meta-analyses of metformin in preventing negative health outcomes/medical conditions in any population and to systematically assess the potential negative outcomes (side-effects) linked to metformin therapy. Our aim is therefore to assess – through an umbrella review ([7](#)) the strength and credibility of the evidence derived from systematic reviews with meta-analyses on metformin for both observational and intervention studies, obtaining a general summary of their importance relative to health outcomes and side effects in any population.

Methods

Protocol

The protocol for this umbrella review is registered on Prospero CRD42018099377. For this umbrella review we followed the PRISMA checklist.[7]

Data sources and searches

We searched the MEDLINE/PubMed, Scopus, Embase and Cochrane Library databases from inception until 31th May 2020 with the following search keywords: "(Meta-Analysis [pt] OR metaanaly*[tiab] OR meta-analy*[tiab] OR Systematic review [pt] OR "systematic review" [tiab]) AND (metformin [tiab])". We further improved the search strategy by including commonly used commercial names of metformin: (Actoplus Met.mp.) or (Metformin/ or Riomet.mp.) or (Metformin/ or Glumetza.mp.) or (Metformin/ or Diabex.mp.) or (Diaformin.mp.)), and the retrieved literature has already been indexed under the MeSH terms of metformin. In addition, we hand-searched the reference lists of eligible articles.

Study selection

We included systematic reviews with meta-analyses of observational studies or meta-analyses of intervention studies, which investigated metformin (any dose but not in combination with other anti-diabetic medications) as putative factor (in observational studies) or intervention (in trials) for any health outcome in any population and any age. For interventions, we considered separately comparisons of metformin versus placebo/no treatment and versus active controls.

For the aims of this work, we have included pairwise meta-analyses, as published in the original works. For network meta-analyses of RCTs, we isolated the network-derived treatment effect for metformin versus placebo/no treatment, or versus active control in separate analyses, to evaluate only direct effects. Meta-analyses that included papers regarding animal or in vitro models, systematic reviews without meta-analyses and conference abstracts were excluded. We included only papers written in English.

Four authors in pairs (SC/DP, MJ/XL) performed the primary screening (i.e., title/abstract screening). When eligibility selection differed, the final decision was taken after consensus with a senior author (JD). The full text screening was performed by two authors (JD, XL).

Data extraction

Extraction work was made on two levels. Four independent investigators organised in two teams (SC/DP, MJ/XL) firstly extracted data from each eligible meta-analysis including PubMed ID or digital objective identifier (DOI), name of the first author, year of publication, study population, number of individual studies included, definition of metformin use, outcome(s) investigated, reported metric and effect size. Then, data from the individual component studies that were included in each eligible meta-analysis were extracted for quantitative analysis. For each individual component study we

extracted: first author name; year of publication; total number of participants included in the study; effect size metric (risk ratio [RR], odds ratio [OR], hazard ratio [HR], incident risk ratio, standardized mean differences (SMDs), MDs) with 95% confidence interval (95% CI); study design (case-control, retrospective, prospective, and RCT); total number of events; total number of controls; number of people randomized to metformin with the correspondent number of events and number of people randomized to placebo/control and correspondent number of events in intervention meta-analyses; follow up time; and metformin dosage, if available.

If two or more meta-analyses were available for the same outcome in the same population, we included the largest in terms of the number of studies. The quality of each meta-analysis was assessed using AMSTAR 2.[8]

Statistical analysis

For each meta-analysis, we estimated the summary effect size and its 95% CIs using the DerSimonian and Laird (DL) random-effects model. As the DL estimator tends to underestimate the 95% CI when a meta-analysis includes a small number of individual studies,[8] we used the modified Hartung-Knapp-Sidik-Jonkman (HKSJ) method [9] for meta-analysis with less than 5 individual studies. For network meta-analyses, we used the estimate derived from consideration of only the direct evidence.The heterogeneity of each meta-analysis was assessed by calculating the I^2 and 95% prediction interval (95% PI).[10, 11] When the fitted model was HKSJ, the percentile of a t-distribution with k−1 degrees of freedom (so the degrees of freedom are not set to zero) was used for the calculation of 95%PI. We used the Egger regression asymmetry test for small-study effects (p-value <0.10).[12] The excess significance test was performed, to evaluate whether the observed number of studies with positive results was significantly greater than the expected number of studies with positive results by using a chi square test.[13] For excess significance test, we calculated the expected number (E) of studies with significant findings by using the sum of statistical power estimated for each component study. The statistical power of each component study was calculated with an algorithm that uses a non-central t distribution, by assuming the true effect size to be the same as that of the largest component study in the meta-analysis. If the type of metric in a meta-analysis was mean difference (MD), we transformed it into OR, and used transformed OR to do the excess significance test. For both the small-study effect and the excess significance tests we used P<0.10 as a threshold. All statistical analyses were conducted in Stata (StataCorp) version 14.0 and all p values are two tailed.

Classification criteria for meta-analyses of observational studies

For observational studies evidence was classified according to the criteria reported in **Table S1**. Following data analysis, the credibility of each meta-analysis was assessed. Observational studies were categorized into four different categories considering several metrics as described previously.[14] Briefly, convincing evidence (class I) was defined as a p-value < 10^{-6}, more than 1000 cases, a statistically significant result reported in the largest individual study, a 95% PI excluding the null value, a heterogeneity below 50% and demonstration of no small study effects and excess

significance bias (p-value > 0.10). Highly suggestive evidence (class II) was assigned to studies reporting a p-value < 10^{-6}, more than 1000 cases and a statistically significant result reported in the largest individual study. Suggestive evidence (class III) was defined as a p-value < 10^{-3} and with more than 1000 cases. Finally, the remaining statistically significant associations with a p-value < 0.05 were classified as weak evidence (class IV).

For associations classified as convincing or highly suggestive, we conducted sensitivity analysis to include studies with follow-up longer than 5 years. Furthermore, we limited the analysis to observational studies with prospective cohort design for associations classified as convincing or highly suggestive. Then, the classification criteria were re-applied to evaluate any changes in the evidence class. If during the in-depth examination of data extraction for each meta-analysis an individual component study was found to be not eligible it was excluded, and evidence was reassessed and compared to the initial results of the meta-analysis. In addition, for associations supported by either Class I and Class II evidence, we used credibility ceilings, a sensitivity analysis tool, assuming that every observational study has a probability c (credibility ceiling) that the true effect estimate could be in a different direction from the one suggested by its point estimate([15], [16]). We selected a relatively lenient credibility ceiling of 10% to reflect the confidence in an observational study. Meta-analysis was rerun using the effect size with the new variance to calculate a new p-val under 10% credibility ceiling.

Criteria for evidence categories for RCTs

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect, using a p-value <0.005 as statistically significant, as recent literature suggests.([17], [18]) All associations with p<0.005 were graded using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment.([19]) Briefly, according to GRADE criteria, we assessed the meta-analysis in terms of risk of bias, imprecision, inconsistency, indirectness, and publication bias, and then rated quality of evidence into four levels: very low, low, moderate, and high.

Criteria for comparison of evidence

In case of overlapping outcomes, investigated in meta-analyses of observational studies and meta-analyses of RCTs, we examined if the direction and statistical significance of associations and respective effects were reported concordantly (or not) across different study types. We noted the overlapping outcomes that were classified as convincing or highly suggestive in meta-analyses of observational studies and had a 95% prediction interval excluding the null in meta-analyses of RCTs or having strong evidence according to the GRADE assessment.

Results

Literature review

Overall, we identified 2,563 papers (**Figure 1**), and 175 publications (corresponding to 427 different meta-analyses, including 167 meta-analyses of observational studies, 147 meta-analyses of RCTs for metformin vs. placebo/no treatment and 113 meta-analyses of RCTs for metformin vs. active medications) were finally included in this umbrella review (all the included meta-analyses are reported in **Supplementary Reference** list).

Meta-analyses of observational studies

As reported in **Table S2**, there is a total of 167 meta-analyses performed for observational studies. The median number of studies included in meta-analyses of observational studies was 5 (interquartile range [IQR]: 3-8), the median number of participants was 3,684 (IQR: 1,134-65,475), and the median number of cases was 702 (IQR: 180-2,620).

The majority of the meta-analyses included studies on mortality or survival outcomes in cancer or diabetic populations (n=80/167, 47.9%), followed by studies on cancer risk/recurrence/metastasis outcomes (n=54/167, 32.3%), obstetric outcomes in pregnant women or women with polycystic ovary syndrome (PCOS) (n=9/167, 5.4%), cognitive outcomes in diabetic and non-diabetic populations (n=5/167, 3.0%), and others (n=19/167, 11.4%). Overall, 80 out of the 167 (47.9%) outcomes reported nominally significant summary results (p<0.05), and 32 associations had $P < 10^{-3}$. There was moderate heterogeneity ($I^2<50\%$) in 67/167 (40.1%) outcomes, moderate to high heterogeneity ($I^2=50\text{-}75\%$) in 49/167 (29.3%) outcomes and high heterogeneity ($I^2>75\%$) in 51/167 (30.5%) outcomes. Altogether, 27 associations over 167 (16.2%) presented 95% PIs excluding the null value. Evidence for excess statistical significance was present in 19 outcomes and for small-study effects in 37/167 (22.2%) of the outcomes. Among outcomes with excess significance, there were 15 meta-analyses in which the largest component study reported a more conservative effect estimate than the summary result.

Based on our credibility criteria, only one outcome presented seemingly convincing evidence in observational studies, i.e. the use of metformin was associated with a lower incidence of pancreatic cancer when compared to sulphonylureas (RR=0.57; 95%CI: 0.51, 0.64, $P=7.29\times10^{-24}$). Four outcomes were classified as seemingly highly suggestive: use of metformin was associated with a lower mortality risk in patients with colon cancer (RR=0.69; 95%CI: 0.61, 0.77, $P=3.09\times10^{-10}$) and patients with heart failure (RR=0.80; 95%CI: 0.74, 0.87, $P=8.41\times10^{-8}$), a lower risk of CVD mortality in diabetic patients (RR=0.44; 95%CI: 0.34, 0.58, $P=2.50\times10^{-9}$), and a lower cancer mortality in the general population (RR=0.68; 95%CI: 0.58, 0.79, $P=7.49\times10^{-7}$), when compared to any other treatment or no treatment, as shown in **Table S2**.

We then performed an in-depth examination for meta-analyses that had seemingly convincing or highly suggestive evidence to evaluate whether these rankings may be spurious. We first checked for the presence of any data anomalies and errors and also conducted these meta-analyses including only prospective cohort studies with follow-up longer than 5 years (if any). Eventually, associations

with reduced incidence of pancreatic cancer, a lower risk of CVD mortality in diabetic patients and a lower mortality risk in heart failure patients were downgraded to have only weak evidence, and associations with a lower risk of cancer mortality in patients with colon cancer and in the general population were found to be even non-significant. Only the association with pancreatic cancer survived the 10% credibility ceiling test. The examination process and results of evaluation are presented in the **Table 1** and **Table S3**.

Meta-analyses of RCTs (vs. placebo/no treatment)

The median number of included RCTs in meta-analyses using placebo/no treatment for each outcome was 3 (IQR: 2-6), the median number of participants was 469 (IQR: 254-840), and the median number of cases was 112 (IQR: 60-213) **(Table S4)**. Overall, 147 meta-analyses were included. The majority of the outcomes included patients taking antipsychotic medications (n=16), outcomes in overweight and obese participants (n=37), and outcomes in PCOS (n=34), type 1 diabetes mellitus (T1DM, n=14) and T2DM (n=13) patients.

Of them, 40/147 (27.2%) meta-analyses reported nominally significant results (p<0.05) and 28/147 (19.0%) were significant at p<0.005, as reported in **Table S4**. **Table 2** shows the GRADE assessment, applied to all outcomes having a p-value <0.005 in the random effects model. Using this tool, we observed a high certainty of evidence that metformin was associated with a lower incidence of diabetes in people having pre-diabetes and in people without diabetes at baseline; with a lower risk of moderate to severe ovarian hyper-stimulation syndrome (OHSS) incidence (in women in controlled ovarian stimulation); with a higher success for clinical pregnancy rate in women affected by PCOS; and with a reduction in BMI in people with T1DM, in obese/overweight women with PCOS and in obese/overweight women in general **(Table 2)**. Heterogeneity among studies was not large (I^2<50%) in 105 of the 147 (71.4%) outcomes. Twenty-one outcomes (21/147, 14.3%) presented 95% prediction interval excluding the null value. Finally, evidence for excess statistical significance was present in 13/147 (8.8%) outcomes and small-study effects were present in 15/147 (10.2%) outcomes.

Meta-analyses of RCTs (vs. active controls)

The median number of included RCTs in meta-analyses including intervention studies using active controls for each outcome was 4 (IQR: 3-7), the median number of participants was 1,256 (interquartile range: 367-3,120), and the median number of cases was 108 (IQR: 35-107) (**Table S5**). The overall number of outcomes using metformin vs. other antidiabetic medications was 113, and five of them are network meta-analyses of RCTs. These outcomes mainly included people with T2DM (n=37), gestational diabetes mellitus (n=36) and PCOS (n=24).

In these meta-analyses, 28/113 (24.8%) outcomes reported nominally significant summary results (p<0.05) and 13 outcomes had p<0.005 (**Table S5**). Using the GRADE assessment for the outcomes having a p-value <0.005, we observed a high level of evidence for a weight gain reduction (when compared to sulphonylureas, MD=3.77 Kg, 95%CI: 3.07-4.47), a lower gestational age at delivery vs.

insulin in gestational diabetes mellitus (SMD=-0.29; 95%CI: -0.46 to 0.12) and a lower incidence of hypoglycemia (when compared to DDP4) (RR=0.45; 95%CI: 0.27-0.74) (**Table 3**).

Heterogeneity among studies was generally moderate, with the majority of outcomes (77/113, 68.1%) having an I^2<50%. However, sixteen outcomes (16/113, 14.2%) presented summary effects with 95% prediction interval excluding the null value. Only six outcomes (6/113, 5.3%) showed evidence for excess significance, whilst 22 outcomes showed evidence for small-study effects.

Overlapping outcomes

Table 4 shows the outcomes for overlapping meta-analyses. Six outcomes were analysed by both meta-analyses of observational studies and meta-analyses of randomised controlled trials, i.e. overall survival in breast and pancreatic cancer, incident prostate cancer in general population, the rate of preterm birth and changes in BMI in PCOS and mortality in T2DM. The direction of the association/effect was in opposite direction for two of the six outcomes. In another three outcomes, direction of association/effect was in the same direction with both designs and both designs had non-significant results. Among the six outcomes included, only for one (changes in BMI in patients affected by PCOS) we observed a significant result with the same direction and with the same magnitude (**Table 4**).

Quality assessment

Seventeen publications included observational and RCT studies, 87 only RCTs and 71 observational studies. Among the 175 publications included, only 4 were rated as high quality according to AMSTAR 2 criteria, 5 as moderate quality, 52 meta-analyses were rated as low quality according to the criteria suggested by the AMSTAR-2, and all the remaining as critically low (n=114). Using this tool, all the meta-analyses of observational studies included were evaluated as having a critically low or low rating (**Table S6**), mainly because the risk of bias was not accurately assessed and the sources of funding for the included studies were not reported. Seventeen of the meta-analyses reported in disclosures the potential funding of authors from industry (i.e., grants, fees for speaking), while it was unclear whether 13 more were funded or not. Overall a potential conflict of interest was detected in 30 meta-analyses (see supplementary **Table S7** for further details), including conflicts due to funding or intellectual conflict of interest.

Discussion

The present work provides a comprehensive overview of the reported associations between metformin and a wide range of health outcomes, in terms of efficacy and safety, by incorporating evidence from meta-analyses of observational and intervention studies.(20-22) This evidence-based umbrella review may be used to help inform decisions about the use of metformin in different settings and populations. Despite a huge number of studies and a stunning total of 427 meta-analyses, evidence on metformin in observational studies generally does not seem very reliable, as can be inferred by substantial heterogeneity between studies, small study effects, and excess significance. While evidence from randomized trials suggests only a few effects with strong evidence for some benefit, but even those may still exhibit other caveats. For example, most of meta-analyses of RCTs did not report information on the follow-up durations and dosage of interventions, making it difficult to evaluate time or dose response effect of metformin use. In addition, there is relatively fewer meta-analyses examining adverse effects as the primary outcome. The only adverse effects examined as primary outcomes were the gastrointestinal events, such as nausea and vomiting, or diarrhea.

One of the main results observed to have high level of evidence in meta-analyses of RCTs (vs placebo or no treatment) is the possible role of metformin in reducing the incidence of diabetes in people having pre-diabetes and in people without diabetes at baseline. The present findings on metformin potentially being prescribed to adults with prediabetes to prevent diabetes mellitus are potentially of clinical importance since the use of metformin is recommended primarily as a first-line anti-diabetic drug, and use in pre-diabetes would expand substantially its use. However, one needs to consider all outcomes as well as cost for decision-making on the use of metformin in pre-diabetes. There have been contrasting views on the use on metformin in prediabetes with ones being against its use arguing that the majority of people with prediabetes do not develop diabetes, approximately one-third return to normal glucose regulation, people with prediabetes are at no increased risk for the microvascular complications of diabetes,(23) and that use of metformin in prediabetes would not improve quality of life, mortality, or any other patient-oriented outcomes.(24) Cautionary note on the widespread use of metformin in prediabetes has also been provided in the recent Cochrane review.(25) Others argued that metformin should be prescribed to selective patients with prediabetes who are at highest risk and most likely to benefit from treatment.(26, 27) This is in line with the 2021 American Diabetes Association Standards of Medical Care in Diabetes that recommend that, in addition to lifestyle counselling, metformin should be considered in people with prediabetes, especially those with BMI of 35kg/m^2 or greater, people younger than 60 years and women with prior gestational diabetes mellitus.(28)

Another key finding from the present review includes the use of metformin for gynecological and obstetrical outcomes. Metformin was associated with a lower OHSS incidence (in women in controlled ovarian stimulation), a higher success for clinical pregnancy rate in women affected by PCOS, a significant reduction of BMI in people with T1DM and in obese/overweight women with PCOS. The results should be interpreted with caution, considering these emerged from reviews rated low or critically low based on AMSTAR2 criteria. Nevertheless, several position statements

indicate that metformin, in addition to lifestyle management, could be recommended to adult women with PCOS, to help improve cardiometabolic and reproductive aspects of PCOS.(29-31) Considering that metformin prescribing in PCOS is generally off-label, health professionals are required to inform women and discuss the evidence, possible concerns and side effects.(31)

Interestingly, the evidence of use of metformin in reducing BMI in women affected by PCOS was the only outcome explored in both observational studies and placebo RCTs, having the same direction and being both statistically significant. In general, metformin has similar pregnancy outcomes to insulin therapy with less maternal weight gain and a high degree of patient acceptability.(32) The possible explanation is that metformin, by reducing insulin resistance, improves maternal and fetal outcomes by reducing maternal obesity and, consequently the related adverse pregnancy outcomes including increased risk of gestational diabetes, preeclampsia, and macrosomia. (32-34)

When compared to active controls, a significant lower weight gain (when compared to sulfonylureas) and a lower incidence of hypoglycemia (when compared to DDP4) was observed with a high level of evidence. Nevertheless, we must consider these findings carefully, as reported in a meta-analysis rated as critically low at the AMSTAR2 assessment. The mechanism for weight loss related to metformin seems to be attributed to its effect on the central nervous system.(35) Metformin may reduce appetite and food intake while total daily energy expenditure remains unaffected owing to its ability to cross the blood brain barrier and act on the hypothalamus through decreases in neuropeptide-Y and agouti-related protein.(35) Two other possible mechanisms include the reduction of insulin resistance in the brain with further lowering of adenosine monophosphate kinase and increasing of proopiomelanocortin which reduces food cravings; and the reduction of adenosine monophosphate kinase activity through the improvement of leptin sensitivity and its secretion reduction.(36) Finally, systemic mechanisms of weight loss include effects on adipose tissue, the gastrointestinal tract and the liver mediated by the activity of adenosine monophosphate kinase that is able to increase the fat oxidation and to decrease lipogenesis through the reduction of circulating lipids, hepatic lipid storage, and hepatic steatosis.(37) The main outcome we observed to be different when comparing metformin and DDP4 was the incidence of hypoglycemia. In contrast to metformin, DDP4 increases the stimulation of insulin and the inhibition of glucagon secretion thought the endogenous GLP-1 levels rise. DDP4 therapy is recommended as second line therapy in case of metformin failure.(38)

Although more than half of the meta-analyses of observational studies showed a statistically significant effect of metformin on different cancer outcomes, none of the meta-analysis of RCTs did. However, there was lower power of meta-analysis of RCTs, justified by a generally lesser number of participants included. In several of the included RCTs, cancer was not the primary outcome but rather an adverse effect.(39-41) Moreover, compared to observational studies, the follow-up period in RCTs is usually shorter, potentially preventing the necessary time for the manifestation of any malignancy.(42)

The most pervasive finding upon assessing the huge literature of metformin meta-analyses was the low or very low quality of the meta-analyses. Most meta-analyses fared very poorly in addressing risk of bias and sources of funding for the included studies. Observational studies are more prone to bias which could also justify the discordance in significance between different meta-analyses. In fact, the five meta-analyses of observational studies that were initially stratified as convincing or highly suggestive were downgraded to be weak or even totally non-significant after restricting the analysis to prospective studies and correcting data anomalies that had been missed by the original systematic reviewers. Reverse causality is a major threat with case-control studies or retrospective cohort studies. The role of reverse causality has been previously suggested in pancreatic and liver cancer, since both types of cancer seem to increase the risk of developing diabetes and therefore of taking metformin.(43) The fact that different comparison groups have been used in different component individual studies to compare the effects of metformin might have also led to some biases. In some cases, metformin users were compared to insulin or sulfonylurea users which are therapies indicated in later stages of the disease. In these cases, the results might be affected by indication bias overestimating the beneficial effects of metformin on cancer outcomes.(44) In some studies, the comparator group was non-diabetic people, which might have underestimated the effects of metformin by ascertainment bias in the diabetic group.(45)

It was not clear whether 30/175 of the meta-analyses were funded by the industry. While metformin is cheap per prescription, it is extremely widely used already, with approximately 80 million prescriptions per year in the USA alone. Many other anti-diabetic agents also are expensive and the total market of anti-diabetics is one of the largest across all types of medications. Therefore, conflicts of interest would need to be carefully dissected in properly interpreting the evidence.

Some additional limitations should be discussed. First, the meta-analyses contained studies that might significantly differ in design, populations, and settings. Heterogeneity in effects may reflect genuine diversity sometimes. Second, many studies in this umbrella review determined the presence of diabetes through self-reported information that, unfortunately, can underestimate the real prevalence of diabetes.(46) Third, some studies reported no metformin as comparison, this has to be acknowledged as a further limitation, as no metformin could encompass different drugs and treatments and it may impair the comparability of studies. Finally, the very low or low quality of most meta-analyses as appraised by AMSTAR 2 suggests that results should be seen with extra caution. Future research in this field would benefit from meta-analyses of higher quality, with particular emphasis on improving the way of bias assessment and providing sources of funding for the included studies.

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