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Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis

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ABSTRACT

This systematic review investigated whether the insulin sensitiser metformin has a geroprotective effect in humans. Pubmed and Embase were searched along with databases of unpublished studies. Eligible research investigated the effect of metformin on all-cause mortality or diseases of ageing relative to non-diabetic populations or diabetics receiving other therapies with adjustment for disease control achieved. Overall, 260 full-texts were reviewed and 53 met the inclusion criteria. Diabetics taking metformin had significantly lower all-cause mortality than non-diabetics (hazard ratio (HR) = 0.93, 95%CI 0.88–0.99), as did diabetics taking metformin compared to diabetics receiving non-metformin therapies (HR = 0.72, 95%CI 0.65–0.80), insulin (HR = 0.68, 95%CI 0.63–0.75) or sulphonylurea (HR = 0.80, 95%CI 0.66–0.97). Metformin users also had reduced cancer compared to non-diabetics (rate ratio = 0.94, 95%CI 0.92–0.97) and cardiovascular disease (CVD) compared to diabetics receiving non-metformin therapies (HR = 0.76, 95%CI 0.66–0.87) or insulin (HR = 0.78, 95%CI 0.73–0.83). Differences in baseline characteristics were observed which had the potential to bias findings, although statistical adjustments were made. The apparent reductions in all-cause mortality and diseases of ageing associated with metformin use suggest that metformin could be extending life and healthspans by acting as a geroprotective agent.

Contents

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1. Introduction

Ageing is characterised by progressive damage at a cellular and organ level as prevention and repair mechanisms begin to break down (Finkel and Holbrook, 2000; Garinis et al., 2008; Mitchell, 2008). Diseases of ageing – such as cardiovascular disease (CVD), kidney failure and cancer – are the result of the accumulation of this damage and ultimately responsible for organisms dying of old age. With the ageing population of the developed world the extension of healthspan – the period that an individual is functional and free of chronic diseases (Barzilai et al., 2016) – has been identified as an important goal both for the minimisation of human suffering and to enable healthcare systems to cope.

One drug which has been subjected to significant research as a geroprotective factor is the insulin sensitiser metformin. Metformin has been shown to extend the lifespans of model organisms (including mice and C. elegans (Anisimov et al., 2011; Anisimov et al., 2010a; Cabreiro et al., 2013)) and a number of potential mechanisms for its effects have been discussed, including decreased insulin and IGF-1 signalling (Liu et al., 2011), inhibition of mTOR (Kickstein et al., 2010; Nair et al., 2014), reducing the levels of reactive oxygen species (ROS)(Batandier et al., 2006; Zheng et al., 2012), lowering inflammation (Saisho, 2015), reducing DNA damage (Algire et al., 2012; Na et al., 2013), and the activation of AMP-activated protein kinase (AMPK)(Zhou et al., 2001). Its effect on AMPK has received particular attention as it models the intracellular mechanisms of caloric restriction (Gillespie et al., 2016; Lee and Min, 2013) – another intervention which has been found to be capable of extending the lifespans of animal models – but which is not feasible for widespread implementation in humans (Roth and Ingram, 2016). This, among other factors, has led to metformin being described as a caloric restriction mimetic (CRM) (Gillespie et al., 2016; Lee and Min, 2013; Roth and Ingram, 2016).

One aspect of metformin which makes it particularly promising for development as a geroprotective agent is that it is already being widely used in humans for a different purpose. As an insulin sensitiser metformin is a first line therapy for diabetes (Nathan et al., 2006). Through this use its potential for adverse effects and contraindications have been well characterised, and it has been found to have a broad safety profile (Rojas and Gomes, 2013) which would make it significantly quicker and easier to implement as an intervention for ageing than a previously unutilised drug.

Due to the widespread application of metformin for the management of diabetes, a large amount of data has already been collected on its effects on mortality and diseases of ageing. However, extrapolation of this research evidence to the general population is invariably confounded by the fact that the people who are currently receiving metformin have diabetes and are taking it for the treatment thereof. As such, any benefits seen could be due to improvements in diabetes control. Two analytic strategies have been attempted to overcome this limitation and gain some insight as to whether metformin could be used to improve the healthspan of the general population.

The first strategy is the comparison of the outcomes of diabetics taking metformin to the general or non-diabetic population (Bannister et al., 2014). This approach reasons that as diabetics are on average less healthy than non-diabetics, superior outcomes in the metformin/diabetic group should be a consequence of beneficial effects of metformin overcoming their generally worse health status. A weakness of this strategy is that people taking metformin could be observed to have worse or the same outcomes as non-diabetics in the presence of an actual beneficial effect of metformin due to it being masked by the detrimental effects of diabetes. The second strategy is to compare diabetics taking metformin to diabetics managing their diabetes through other means while statistically controlling for the effects of the different therapies on diabetes management (i.e. HbA1c or diabetes related doctor visits (Lin et al., 2015)). This strategy reasons that any difference in outcomes seen after adjusting for the relative effects on disease management can be attributed to metformin's activity beyond diabetes control, and are therefore generalisable. This strategy's weaknesses are that statistical adjustment is an imperfect process – it is always possible that residual confounding remains that could cause any differences observed – and that other antidiabetic drugs could cause harms which in comparison would appear to be beneficial effects by metformin.

However, although additional controlled, experimental research will need to be carried out, there exists a wealth of observational data that can offer evidence on whether metformin could be applied as a geroprotective agent in humans. As such, this systematic review and meta-analysis has been undertaken to identify and synthesise all studies where the effects of metformin on all-cause mortality or diseases of ageing have been compared to the general or non-diabetic population or to diabetics managing their diabetes through other means with adjustment for disease control. Numerous systematic reviews have been carried out which nominally address this review's outcomes of interest, however those which investigate the association between metformin and all-cause mortality do so in the context of severe diseases in addition to diabetes (usually various forms of cancer) (Coyle et al., 2016; Gash et al., 2017; Li et al., 2017; Meng et al., 2017; Tang et al., 2017; Zhou et al., 2017a) and their results therefore cannot be generalised, while those that investigate the incidence of diseases of ageing do so without attempting to adjust for diabetes control (Liu et al., 2017; Ma et al., 2017; Pladevall et al., 2016; Tang et al., 2017; Zhou et al., 2017b). As such, the question of whether metformin could act as a geroprotective agent in humans has yet to be addressed in a systematic review.

2. Methods

2.1. Objective

This systematic review aimed to identify and synthesise all research on the effect of metformin on all-cause mortality and diseases of ageing which had the potential to give evidence on whether it could be used as a geroprotective factor to extend life and healthspan in the general population. It followed an *a priori* protocol pre-registered with PROSPERO (CRD42016036098).

2.2. Inclusion criteria

2.2.1. Population

Studies on all-cause mortality were eligible for inclusion if they reported on adults with a minimum age of 40 years or a mean age of 50 years. This age restriction was applied to increase the proportion

of deaths which would be attributable to age and was not applied to studies on diseases of ageing. Studies were included where metformin was being given to patients for the treatment of a particular disease (diabetes in all cases although this was not an inclusion criterion), however where populations were specifically selected to include a second serious illness (i.e. patients with cancer who were also being treated for diabetes), studies were not eligible for inclusion.

2.2.2. Exposure

Studies were included where a group of patients had been treated with metformin of any dosage taken on an ongoing basis.

2.2.3. Comparator

Any controls were eligible for inclusion provided they were not receiving metformin. This included members of the general or non-diabetic population as well as people who were receiving other therapies for diabetes. In the latter case, studies were only included if data was adjusted for the effect of diabetes on disease control (i.e. HbA1c levels or number/rate of diabetes related healthcare visits). Where patients entered into studies were using metformin on an ongoing basis their data was included if diabetes control at baseline was adjusted for, as this reflected how well their diabetes was being managed by metformin. However, if patients were enrolled with incident metformin use and the only adjustment for disease control was made at baseline, the study was excluded as this data would not reflect the effect of metformin.

2.2.4. Outcomes

The two primary outcomes were all-cause mortality and the incidence, onset or prevalence of diseases of ageing. Studies on disease specific mortality were not eligible for inclusion. Any diseases of ageing were eligible for inclusion with the exception of diabetes as any effect metformin had on diabetes incidence could more likely be attributed to it directly treating pre-diabetes as an insulin sensitiser than extending healthspan. Diseases ultimately included were cancer (including breast, lung, colorectal, pancreatic, prostate, oesophageal, thyroid, renal, hepatocellular, and head and neck cancer), CVD (including stroke, myocardial infarction, heart failure, coronary heart disease, macrovascular morbidity and ventricular dysfunction), kidney failure, fracture, open angle glaucoma, cognitive impairment, and carpal tunnel syndrome.

2.2.5. Studies

Both experimental and observational studies (including cohort, case-control and analytical cross-sectional studies) were eligible for inclusion in this systematic review. Case report and case series studies were ineligible.

2.3. Search strategy

The search for published literature included Pubmed and Embase, while the search for unpublished studies included the International Clinical Trials Registry Platform, ProQuest Dissertations and Theses Global, and OpenThesis. No date restrictions were applied, however only English language articles were eligible for inclusion. The search was carried out in March 2016. Full details of the structure and content of each search undertaken are reported in supplementary material 1. Titles and abstracts were screened followed by the retrieval of potentially relevant full-texts. These were then carefully compared to the inclusion criteria to identify eligible studies. The reference lists of included full-texts were then reviewed, however no additional studies that met the inclusion criteria were identified.

2.4. Appraisal and extraction

Duplicate critical appraisal was carried out using the standardised Joanna Briggs Institute (JBI) appraisal checklists for experimental, cohort, case control and cross-sectional studies (The Joanna Briggs Institute, 2014) by independent reviewers working separately, with consensus reached through discussion in all cases. Data was extracted for all studies using an extraction template which included fields for; study methodology, study design, inclusion criteria, data source, country, disease control, exposure, comparator, sample size/events, follow up, outcome(s), outcome data, and statistical adjustments. Where additional data or clarification was needed, attempts were made to contact corresponding authors by email.

2.5. Data synthesis

Where possible, data was pooled through meta-analysis. The inverse variance method with a random effects model from RevMan was used, unless otherwise specified. Data included in the meta-analyses was always from the analyses with the greatest adjustment. Where summary measures differed, outcomes were converted to hazard ratios (HRs) using the equations described in Tierney et al. (2007). Data were analysed separately based on comparators utilised, and heterogeneity was assessed using the Chi^2 and I^2 tests. Two sets of sensitivity analyses were carried out where poor quality studies (<70% on critical appraisal) were removed from meta-analyses, and where studies that did not adjust for duration of diabetes and/or comorbidities were removed. Analysis of publication bias through Funnel plots and Egger's test was planned if sufficient studies (at least 10) were found for any outcomes, however none were. Where statistical pooling was not possible data is presented narratively.

3. Results

The initial search identified a total of 21,027 studies, which was reduced to 19,408 following the removal of duplicates. Following title/abstract screening, 260 studies were included for full-text review. Of these, 207 were excluded and 53 were included. Full search details and reasons for exclusion are given in Fig. 1. Overall, 13 included studies reported data on all-cause mortality while 49 reported on diseases of ageing.

3.1. All-cause mortality

Of the studies that investigated the effect of metformin on all-cause mortality, four compared diabetic patients being treated with metformin to the general population or non-diabetic patients (Bannister et al., 2014; Berard et al., 2011; Bo et al., 2012; Claesen et al., 2016), while nine compared diabetic patients being treated with metformin to diabetic patients managing their diabetes through other means. Subgroups within the latter group included insulin therapy (Ekstrom et al., 2012; Ghotbi et al., 2013), diet interventions (Bo et al., 2012; Sullivan et al., 2011), sulphonylurea therapy (Evans et al., 2006; Kahler et al., 2007; Sullivan et al., 2011; Wang et al., 2014), and non-metformin therapies (studies assigned to this group included all patients receiving any other oral hypoglycemic agent, but may have also included those receiving insulin, diet, or no therapy as well) (Ekstrom et al., 2012; Ghotbi et al., 2013; Gosmanova et al., 2008; Libby et al., 2009; Pratipanawatr et al., 2010). Full details of interventions, controls and other study characteristics are included in Table 1. For the metformin versus non-diabetic comparison three of the cohorts were matched by age (Bannister et al., 2014; Bo et al., 2012; Claesen et al., 2016) while in the fourth (Berard et al., 2011) metformin users were

Table 1
Characteristics of studies investigating the effect of metformin on all cause mortality.

Study	Exposure	Comparator	Population	Diabetes control adjustment	N/events and Follow up	Covariates adjusted for in multivariable analysis
Metformin compared to Non-Diabetic or General Population						
Bannister et al. (2014)	Metformin initiation	Non diabetic matched for age, gender, same general practice, prior cancer status and smoking status	United Kingdom. Cohort. Incident diabetes and exposed to glucose lowering therapy for a minimum of 180 days (excluded if any record of secondary diabetes).	N/a	Metformin = 78,241/2663 Non-diabetic = 78,241/2669 deaths Mean: 2.8 years	Age, modified Charlson index, gender, smoking status, prior antiplatelet therapy, prior lipid-lowering therapy, prior antihypertensive therapy, year of study index date and study arm.
Berard et al. (2011)	Metformin use at baseline	Non diabetic at baseline	France. Cohort. Middle aged men and women with diabetes. Exposure (hypoglycaemic drug use, presence of metformin) was assessed at entry only.	N/a	Metformin = 40/9 Non-diabetic = 3162/213 14 years	Duration of diabetes, history of diabetes complications, area of residence, age, gender, educational level, alcohol consumption, smoking, blood pressure, LDL and HDL cholesterol.
Bo et al. (2012)	Metformin use	General population based on age and sex	Italy. Cohort. Patients with type 2 diabetes.	N/a	Metformin = NR/104 General population = NR/128 Mean = 4.5 years	None.
Claesen et al. (2016)	Metformin use at baseline (censored if discontinued for more than 9 months)	Non users of glucose lowering agents	Belgium. Cohort. Patients older than 18 prescribed metformin and non users of glucose lowering agents matched 5 to one on age, gender, cardiovascular history, associated therapies and year of start of follow up.	N/a	Metformin = 42,900/3389 Non diabetic = 214,500/16,517 5 years	Adjusted for age, associated therapies, and gender.
Metformin compared to other diabetes therapies, controlling for diabetes management						
Bo et al. (2012)	Metformin use	Management of diabetes through diet alone	Italy. Cohort. Patients with type 2 diabetes.	HbA1c	Metformin = 1479/136 Diet = 620/68 Mean: 4.5 years	Adjusted for propensity score which included: propensity score which included: age, sex, diabetes duration, HbA1c, smoking, BMI, retinopathy, nephropathy, coronary or peripheral artery disease, other comorbidities, use of hypertensives, use of acetylsalicylic acid
Ekstrom et al. (2012)	Metformin use continuously for 12 months before baseline	Insulin use continuously for 12 months before baseline *Or* Other OHA *Or* Insulin and other OHA	Sweden. Cohort. Men and women aged 40–85 with type 2 diabetes on continuous glucose lowering treatment that filed at least 3 prescriptions for their treatment (or 18 fills of multi-dose dispensed drugs) in the 12 months before baseline.	HbA1c at baseline (at least 1 year after treatment commencement)	Metformin = 14,697/1734 Insulin = 12,291/2389 Other OHA = 5171/020 Insulin and other OHA = 1365/NR Mean: 3.9 years	Age, sex, diabetes duration, HbA1c, non-HDL-C, BMI, smoking, eGFR, multidose dispensation, previous hospitalisation, history of CVD and CHF, microalbuminuria, and treatment with antihypertensive agents, lipid lowering agents, and cardiac glycosides

Evans et al. (2006)	Metformin monotherapy throughout study period (initiated at baseline, censored from date of switch to new therapy)	Sulfonylurea monotherapy throughout study period (initiated at baseline, censored from date of switch to new therapy)	United Kingdom. Cohort. Patients with type 2 diabetes newly prescribed OHAs.	Average HbA1c for the study period	Metformin = 2286/107 Sulphonylurea = 3331/597 NR	Gender, Age, Diabetes duration, previous CV hospitalisation, Smoking, mean HbA1c, mean BMI, mean systolic blood pressure, mean diastolic blood pressure, mean cholesterol, using aspirin, using statins, using beta blockers, using ACE inhibitors.
Ghotbi et al. (2013)	Metformin monotherapy *Or* Metformin with insulin	Insulin monotherapy *OR* Any other therapy (Diet, insulin, sulphonylureas) alone or in any combination	Worldwide (16 countries). Cohort. Patients who were 55 years or over with BMI 27–45 with diabetes.	Change in HbA1c values And/or HbA1c levels	Metformin = 1631/96 Metformin with insulin = 1000/88 Insulin = 1116/138 Any other therapy = NR	Age, smoking habits, diabetes duration, congestive heart failure, history of hypertension, BMI, sex, history of CVD, tobacco use, HDL concentrations, LDL concentrations, change in HbA1c values and/or HbA1c levels, heart rate, actual systolic and diastolic blood pressure, sibutramine usage
Gosmanova et al. (2008)	Metformin (combination or montherapy)	Not receiving metformin	USA. Cohort. Veterans with type 2 diabetes receiving long term care at veterans affair medical center treated with a prescription claim for oral hypoglyemic agents	HbA1c at baseline (treatment was ongoing)	Metformin = 1207/266, Non-metformin = 999/253 Metormin = 62 months, Non-metformin = 61 months	Age, race, eGFR, HbA1c, use of insulin, ACEI/ARBs, or statins.
Kahler et al. (2007)	Metformin montherapy Metformin with sulphonylurea	Sulfonylurea monotherapy	USA. Cohort. People with diabetes at least 18 years of age who survived at least 1 year after drug assessment.	HbA1c at baseline (treatment was ongoing)	Metformin = 2988/82 Metofrmin with sulphonylurea = 13,820/468 Sulphonylurea = 19,053/1005 NR	Age, diabetes suration, HbA1C, creatinine, diabetes related physician visits and also a propensity score constructed from 48 variables.
Libby et al. (2009)	In receipt of a metformin prescription	No record of metformin use, matched by year of diagnosis	United Kingdom. Cohort. Patients diagnosed with type 2 diabetes aged 35 or over.	HbA1C during the study period	Metformin = 1085/609 Non-metformin = 4085/1422 NR	Age, sex, smoking, deprivation, BMI, A1C, insulin use, sulphoylurea use.
Pratipanawatr et al. (2010)	Metformin use	Non use of metformin	Thailand. Cohort. Diabetic patients receiving clinic treatment	HbA1C at baseline (treatment was ongoing)	Overall = 9370/424 3 years	Age, sex, HbA1c, serum creatinine, healthcare plan, education staus, smoking status, previous history of coronary artery disease and cerebrovascular disease, lipid lowering medication, insulin.
Sullivan et al. (2011)	Metformin montherapy	Diet alone *Or* Sulphonylurea monotherapy	International. Cohort. Patients with type 2 diabetes	HbA1c at baseline (treatment was ongoing)	Metformin = 1746/NR Diet = 1632 Sulphonylurea = 1632 5 years	Age, sex, duration of diabetes, smoking, waist-hipratio, systolic blood pressure, total cholesterol, HDL cholesterol, HbA1c, ACR group, history of CVD, presence ofmicrovascular disease, creatinine and peripheral damage to feet.
Wang et al. (2014)	Metformin prescription as sole class of glucose lowering medication for ≥180 days	Sulfonylurea prescription as sole class of glucose lowering medication for ≥180 days	USA. Cohort. Veterans aged 65–89 years with type 2 diabetes without history of liver, renal diseases, or cancers	HbA1c during the study period	Metformin = 307/NR Sulphonylurea = 2108 Mean = 5.6 years	Age, race, diabetes duration, age adjusted Charlson co-morbidity, smoking cessation status, mean LDL across study period, mean HbA1c across study period and propensity score.

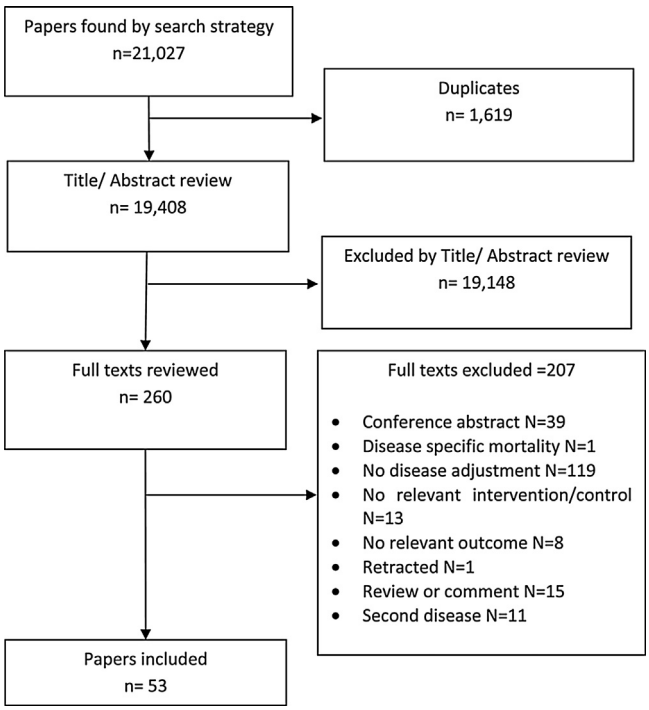

Fig. 1. PRISMA flow chart.

older (mean ± SD age 56.2 ± 6.6) than non-diabetics (50.1 ± 8.3); a disparity which could be expected to bias the results towards a finding of metformin being associated with increased mortality, although age was adjusted for. In the majority of cases when metformin users were compared to other diabetics, metformin users were younger (Ekstrom et al., 2012; Evans et al., 2006; Ghotbi et al., 2013; Gosmanova et al., 2008; Kahler et al., 2007; Sullivan et al., 2011; Wang et al., 2014). Differences between mean ages ranged from 0.4 years (Gosmanova et al., 2008) to 5.9 years (Ekstrom et al., 2012). In one study the metformin group was older than the control by <1 year (Bo et al., 2012), and in two mean ages were not reported (Libby et al., 2009; Pratipanawatr et al., 2010), although Libby et al. did match by year of diagnosis so age is likely to have been close. The trend of metformin users being younger than other diabetics has the potential to bias results towards a finding of decreased mortality, however all studies adjusted for age, with the exception of Bo et al. The appraisal of study quality found that overall the studies were conducted rigorously, with notable deficiencies being that none reported similar characteristics in their respective populations at baseline and less than half had adequate follow up times for our observations of interest (defined as ≥5 years) with thorough reporting on reasons for loss to follow up (Supplementary material 2).

Meta-analysis of the four studies that compared people managing their diabetes with metformin to non-diabetics or the general population (Bannister et al., 2014; Berard et al., 2011; Bo et al., 2012; Claesen et al., 2016) found that people taking metformin had significantly lower mortality compared to those who were not (Fig. 2 HR = 0.93, 95%CI 0.88–0.99, p = 0.03). One included study was an outlier in that it reported a non-significant increase in mortality for people taking metformin (Berard et al., 2011), however it was by far the smallest study, with just nine events in the metformin group. Hazard ratios (HRs) used in the meta-analysis represent adjusted values with two exceptions where the HR could only be calculated for crude data (Bannister et al., 2014) and where only crude analyses were performed for this data (Bo et al., 2012). Sensitivity analysis could not be carried out as no studies were of poor quality and only one study adjusted for diabetes duration and/or comorbidity.

The finding that metformin reduces mortality was supported by analyses that compared diabetic patients receiving metformin to diabetic patients receiving other therapies (Fig. 3), where diabetes control had been adjusted for.

The majority of subgroups, including studies with non-metformin controls (HR = 0.72, 95%CI 0.65–0.80, p < 0.00001), insulin treated controls (HR = 0.68, 95%CI 0.63–0.75, p < 0.00001), and sulphonylurea treated controls (HR = 0.80, 95%CI 0.66–0.97, p = 0.02), found that even after adjusting for metformin's effect on diabetes control, diabetics taking it had lower all-cause mortality than diabetics who were not. The one exception was the subgroup where the controls managed their diabetes through diet alone. In this case one study (Bo et al., 2012) found a significant benefit to all-cause mortality for metformin and the other study (Sullivan et al., 2011) found a non-significant disadvantage resulting in an overall non-significant finding (HR = 0.91, 95%CI 0.68–1.22, p = 0.53). An overall meta-analysis could not be performed as the same studies were included across multiple subgroups where they presented their metformin data relative to different controls. However, when the duplicate data sets were excluded (removing those with the strongest positive findings: Ekstrom Non-Metformin, Ghotbi Non-Metformin and Sullivan Sulphonylurea), diabetics taking metformin had significantly lower mortality compared to controls after adjusting for disease control (HR = 0.75, 95%CI 0.69–0.82, p < 0.00001). Sensitivity analysis for the non-metformin control subgroup where two studies which did not adjust for duration of diabetes and/or comorbidity were excluded (Gosmanova et al., 2008; Libby et al., 2009) did not affect results. Sensitivity analysis for study quality could not be performed as no studies were poor quality.

3.2. Diseases of ageing

The main diseases of ageing investigated in the included studies were cancer (Supp Table S1) and cardiovascular disease (CVD, Supp Table S2). However, other age related conditions were investigated in a smaller number of studies including renal failure, fracture, open angle glaucoma, cognitive impairment and carpal tunnel syndrome (Supp Table S3).

3.2.1. Cancer

Overall, 25 studies investigated the association between metformin use and cancer (Supp Table S1). Where people taking metformin were compared to the general or non-diabetic population the majority of studies did not report the ages of these groups. The two that did found that people taking metformin were significantly older (Andersson et al., 2012; But et al., 2014), potentially biasing the results to increased risk of cancer in metformin users although age was adjusted for in both analyses. Amongst the remainder of studies half were case-controls which matched for age and are therefore unlikely to have meaningful hidden bias (Becker et al., 2014, 2016; Bodmer et al., 2012a; Bodmer et al., 2012b; Lu et al., 2015; Walker et al., 2015) and the remainder adjusted for age (Baur et al., 2011; Becker et al., 2013; Nordström et al., 2015; Tseng, 2011, 2012a, 2012b). For people taking metformin compared to diabetics controlling their diabetes through other means, only one study reported relative ages for the comparison (metformin users were younger biasing results towards a lower risk of cancer although age was adjusted for (Goossens et al., 2015)). Nine studies were case-controls which matched for age and therefore have limited risk of bias in this regard (Azoulay et al., 2011; Becker et al., 2013; Bodmer et al., 2010; Bosco et al., 2011; Chen et al., 2013; Mazzone et al., 2012; Sehdev et al., 2015; Smiechowski et al., 2013a, 2013b), while two cohort studies adjusted for age but did not

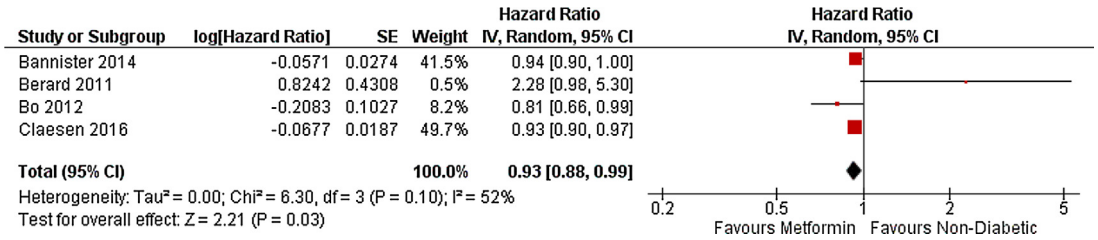

Fig. 2. All-cause mortality hazard ratios in people using metformin for diabetes compared to the general or non-diabetic population.

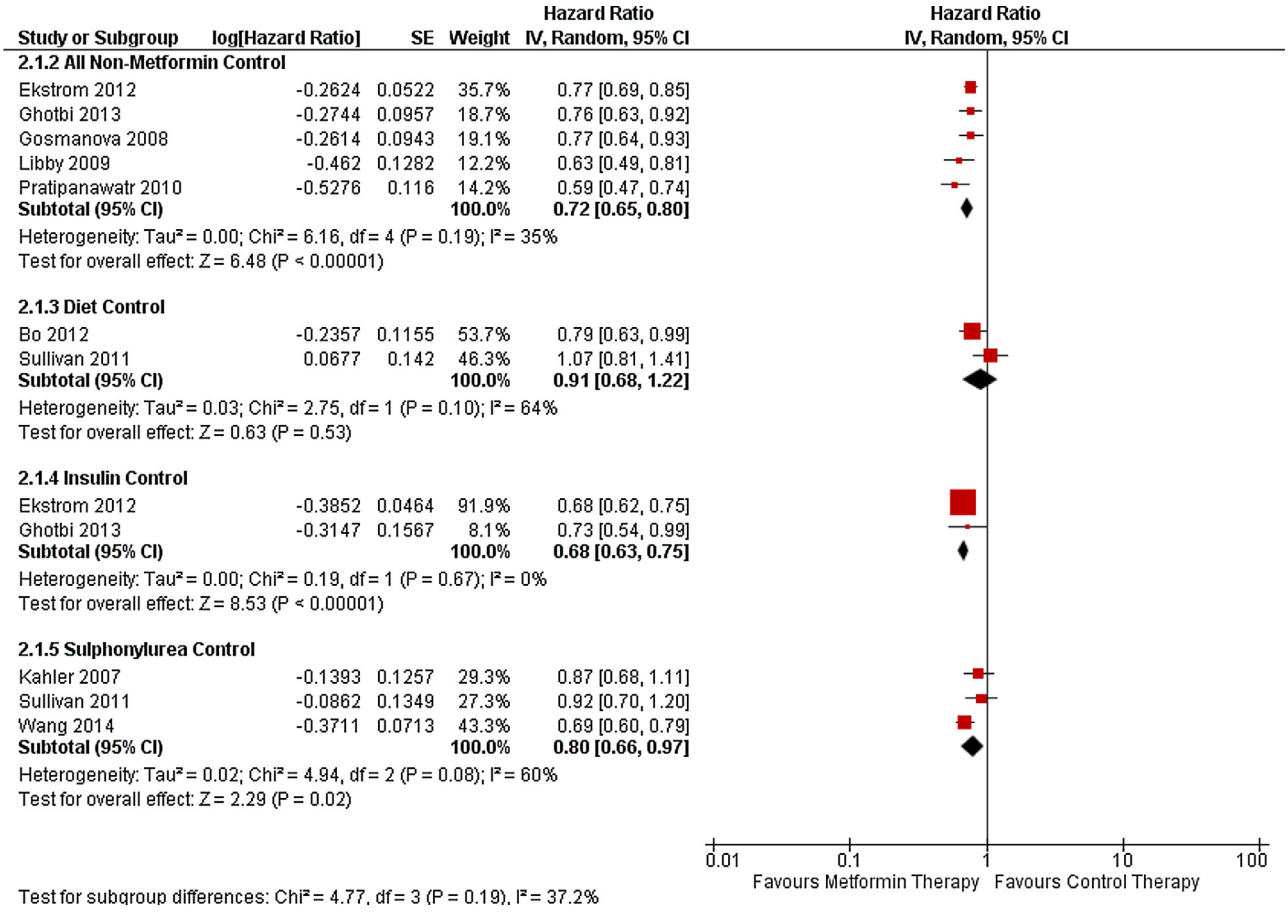

Fig. 3. All-cause mortality hazard ratios in people using metformin for diabetes compared people using other therapies for diabetes. 2.1.2 'All Non-Metformin Control' includes studies where the controls were any diabetic people receiving who were not being treated with metformin (or controls which were receiving a broad range of therapies). 2.1.3 'Diet Control' includes studies where controls were managing their diabetes though diet. 2.1.4 'Insulin Control' includes studies were controls were managing their diabetes using insulin. 2.1.5 'Sulphonylurea' includes studies where controls were managing their diabetes using sulphonylurea.

report it (Libby et al., 2009; Redaniel et al., 2012). Critical appraisal showed that cohort studies compared groups with significant differences at baseline, tended to lack adequate follow up and did not report on reasons for loss to follow up with similar deficiencies observed in case-control studies (supplementary material 2). Of the included studies, three investigated the incidence of any cancer for people taking metformin for diabetes control compared to non-diabetics. Two of these studies could be combined in meta-analysis (Fig. 4A, (Andersson et al., 2012; But et al., 2014)) and showed that diabetics taking metformin had significantly lower cancer incidence (Rate ratio = 0.94, 95%CI 0.92–0.97, p = 0.0003). In this case rate ratio was used in the meta-analysis rather than HR as both studies used it as the summary measure to report their data. It should be noted that although there was essentially no heterogeneity between the two studies, the results of the meta-analysis drew almost entirely on the findings of (Andersson et al., 2012) which received 99% of the weight. The third study (Baur et al., 2011) was cross-sectional and found a non-significant decrease in the prevalence of cancer in diabetics receiving metformin monotherapy compared to the non-diabetic population, and a non-significant increase in diabetics receiving metformin as a combination therapy. A fourth study investigated the effect of metformin on cancer incidence but compared it to matched diabetics receiving any other oral hypoglycaemic agent rather than non-diabetics (Libby et al., 2009). It reported a significant reduction for metformin (HR = 0.63, 95%CI 0.53–0.75, p < 0.05), supporting the findings of the meta-analysis.

Three studies investigated the effect of taking metformin on the development of pancreatic cancer in people with diabetes compared to the general (Bodmer et al., 2012b; Lu et al., 2015) or non-diabetic population (Walker et al., 2015). However, findings were mixed and the result of the meta-analysis was non-significant (Fig. 4B, all studies reported their outcomes as odds ratios (ORs),

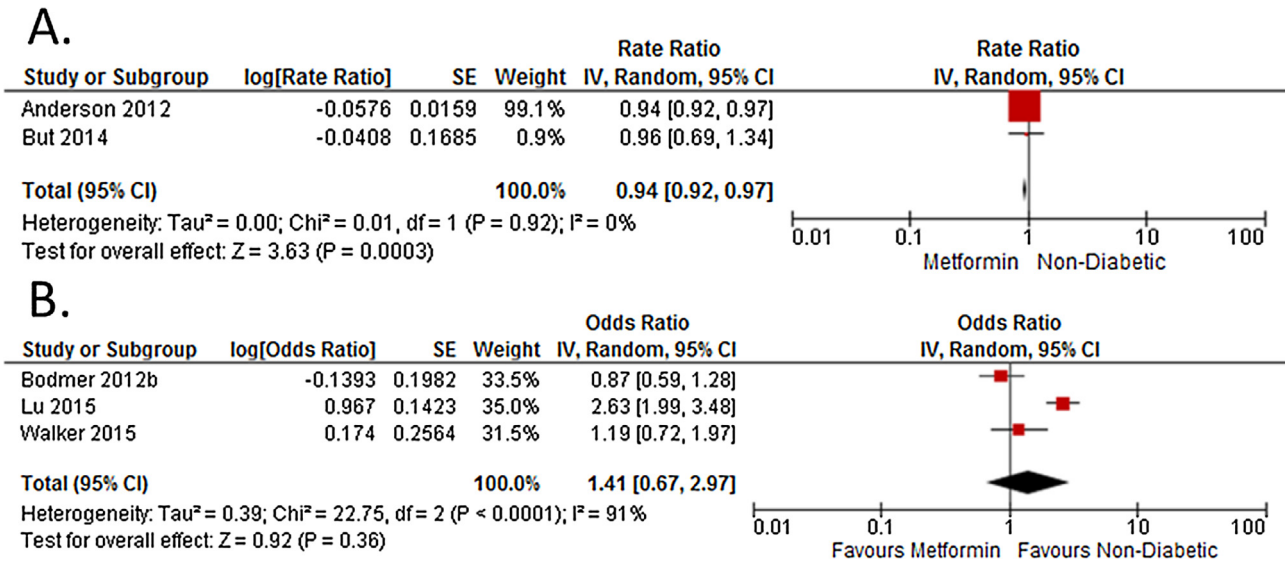

Fig. 4. A) Cancer incidence in people with diabetes taking metformin compared to the general or non-diabetic population. B) Pancreatic cancer incidence in people with diabetes taking metformin compared to the general or non-diabetic population.

therefore this was the summary measure used in the meta-analysis). Sensitivity analysis could not be carried out as no studies were of poor quality and only one study adjusted for duration of diabetes and/or comorbidity.

The effect of metformin on the incidence of colorectal cancer was investigated in four studies, three of which were similar enough to be combined in meta-analysis (Libby et al., 2009; Sehdev et al., 2015; Smiechowski et al., 2013a). These studies compared the incidence of colorectal cancer in diabetic patients taking metformin to non-metformin diabetic controls. Although a trend for metformin use being associated with a reduced incidence of colorectal cancer was found, the results were ultimately non-significant (Fig. 5A, HR = 0.85, 95%CI 0.72–1.02, p = 0.08). As heterogeneity was non-significant ($Chi^2 = 0.15$, $I^2 = 48\%$) and all studies suggested a benefit, a meta-analysis using the fixed effects model was trialled. A significant reduction in colorectal cancer incidence for the metformin group was found (HR = 0.91, 95%CI 0.84–0.98, p = 0.009). Sensitivity analysis where one study which did not adjust for duration of diabetes and/or comorbidity was excluded (Libby et al., 2009) did not have a large effect on the estimate but resulted in a significant finding by the random effects model (HR = 0.92, 95%CI 0.85–0.99, p = 0.02). Sensitivity analysis for study quality could not be performed as no studies were poor quality. An additional study not included in the meta-analysis (Tseng, 2012a) compared the incidence of colorectal cancer in diabetics taking metformin to the general population and found that metformin was associated with a significant reduction (relative risk = 0.73, 95%CI 0.58–0.92, p = 0.008), supporting the conclusion that metformin may reduce colorectal cancer incidence.

Breast cancer incidence was investigated in four studies, three of which compared the incidence in diabetic patients taking metformin to diabetic patients who were not taking metformin (Bodmer et al., 2010; Bosco et al., 2011; Libby et al., 2009). These were combined in meta-analysis Fig. 5B which showed a significant reduction in the incidence of breast cancer (HR = 0.71, 95%CI 0.54–0.92, p = 0.01). Sensitivity analysis where one study which did not adjust for duration of diabetes and/or comorbidity was excluded (Libby et al., 2009) did not have a large effect on the estimate but resulted in a non-significant finding being made (HR = 0.72, 95%CI 0.50–1.04, p = 0.08). Sensitivity analysis for study quality could not be performed as no studies were poor quality. The fourth study compared the incidence of breast cancer in diabetics being treated with metformin to diabetics being treated with sulphonylurea (Redaniel et al., 2012) and found a non-significant increase in breast cancer for metformin. Interestingly, they also compared people taking metformin in combination with sulphonylurea to people taking sulphonylurea alone and found a significant reduction in the incidence of breast cancer in the people treated with metformin (HR = 0.66, 95%CI 0.50–0.88, p < 0.05).

The effect of metformin on the incidence of lung cancer was investigated in four studies. Three studies compared the incidence of lung cancer in diabetic patients treated with metformin to diabetic patients not treated with metformin (Libby et al., 2009; Mazzone et al., 2012; Smiechowski et al., 2013b) and could be combined in meta-analysis Fig. 5C. The combined results showed that taking metformin was associated with a decreased incidence of lung cancer in diabetic patients (HR = 0.80, 95%CI 0.65–0.98, p = 0.03). Sensitivity analysis could not be carried out as no studies were of poor quality and only one study adjusted for duration of diabetes and/or comorbidity. The fourth study (Bodmer et al., 2012a) compared diabetics taking metformin to the general population. It did not find any significant effects for short term (1–14 prescriptions) or long term (≥40 prescription) metformin use, however medium term (15–39 prescriptions) metformin use was contradictorily associated with a significant increase in the odds of developing lung cancer (OR = 1.24, 95%CI 1.03–1.50, p < 0.05).

Additional cancers that were investigated included prostate, bladder, thyroid, renal, head and neck, oesophageal, and hepatocellular cancer. Neither of the two studies on prostate cancer found any significant association with metformin use (Azoulay et al., 2011; Nordström et al., 2015). Nor did the studies on bladder cancer (Goossens et al., 2015; Tseng, 2011), thyroid cancer (Tseng, 2012b), renal cell carcinoma (Becker et al., 2016), head and neck cancer (Becker et al., 2014), or oesophageal cancer (Becker et al., 2013). However, metformin users had significantly lower odds of developing hepatocellular cancer compared to other diabetics (OR = 0.79, 95%CI 0.75–0.85, p < 0.0001).

3.2.2. *Cardiovascular disease*

Fifteen studies were found that investigated the effect of metformin on the development of CVDs (Supp Table S2). Critical appraisal showed a similar pattern in quality as observed for studies on all-cause mortality and cancer – groups had significant differences at baseline, follow-up was frequently shorter than desirable

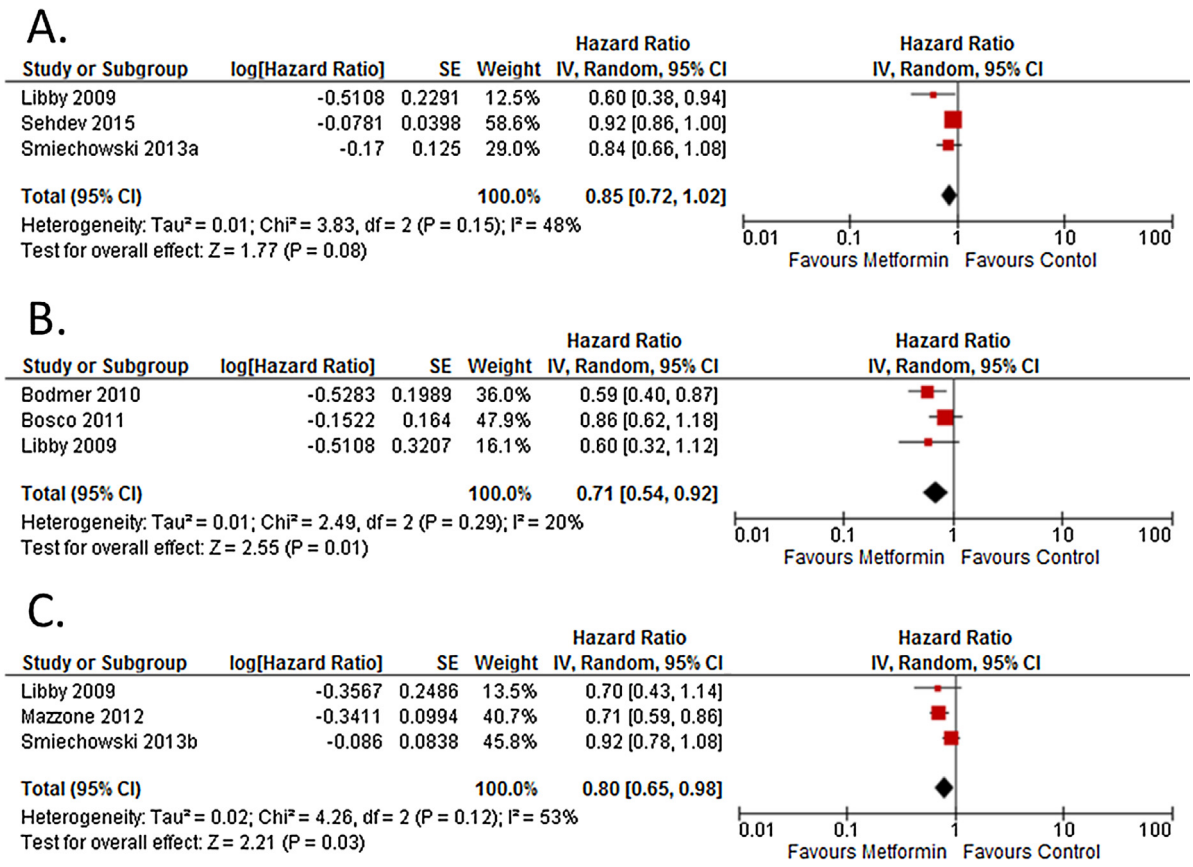

Fig. 5. A) Colorectal cancer incidence for people with diabetes taking metformin compared to diabetics not taking metformin. B) Breast cancer incidence for people with diabetes taking metformin compared to diabetics not taking metformin C) Lung cancer incidence for people with diabetes taking metformin compared to diabetics not taking metformin.

to observe the onset of disease, and loss to follow up was inadequately described (Supplementary material 2). Additionally, over half of the cohort studies included participants who already had some form of CVD at baseline and half of the case-control studies did not adequately control for potential confounding factors. No studies compared people taking metformin for diabetes management to non-diabetics or the general population. For those that compared people taking metformin to people controlling their diabetes through other means, six included analyses where the group receiving metformin was younger than those who were not (Ekstrom et al., 2012; Evans et al., 2006; Ghotbi et al., 2013; McAlister et al., 2008; Sullivan et al., 2011) (the difference ranged from 1.1 years) (Sullivan et al., 2011) to 5.9 years (Ekstrom et al., 2012), while in two studies people receiving metformin were younger than comparators (2.8 years (Nichols et al., 2005) and 5 years (Kooy et al., 2009)). Three further studies were case-controls which matched for age (Floyd et al., 2016; Hartung et al., 2005; Koro et al., 2005) while four did not report on relative ages but did adjust for age in their analyses (Gejl et al., 2015; Giorda et al., 2011; Jansson et al., 2014; Peters et al., 2013). Five studies comparing the incidence of any CVD in diabetics taking metformin to diabetics not receiving metformin could be combined in meta-analysis (Ekstrom et al., 2012; Gejl et al., 2015; Ghotbi et al., 2013; Jansson et al., 2014; Peters et al., 2013). This showed a significant reduction in CVD for people taking metformin (Fig. 6, HR = 0.76, 95%CI 0.66–0.87, $p < 0.0001$). Sensitivity analysis where studies of low quality were excluded from meta-analysis did not have a large impact on the estimate (HR = 0.73, 95%CI 0.53–1.00, $p = 0.05$). No studies did not adjusted for duration of diabetes and/or comorbidity. The finding of a reduction was supported by two studies that compared the incidence of any CVD between diabetics being treated with metformin to diabetics treated with insulin (Ekstrom et al., 2012; Ghotbi et al., 2013), where a significant decrease in incidence with metformin use was found (Fig. 6, HR = 0.78, 95%CI 0.73–0.83, $p < 0.00001$). However, the meta-analysis for sulphonylurea controls, which also included two studies (Evans et al., 2006; Sullivan et al., 2011), did not show a significant effect (Fig. 6). One study was found that investigated the effect of metformin on incidence of CVD compared to diabetics managing their diabetes through diet and showed a non-significant increase in the metformin group (Sullivan et al., 2011). An overall meta-analysis was prevented as the subgroups contained data from the same participants. However, when duplications were removed (again excluding the data that showed the strongest positive effect: (Ekstrom Non-metformin, Ghotbi Non Metformin, Sullivan Diet), the result was a significant effect for metformin reducing the incidence of CVD (HR = 0.83, 95%CI 0.73–0.94, $p = 0.004$).

Three studies investigated the effect of metformin on the incidence of stroke. Two compared the incidence of stroke in metformin users to other diabetics not using metformin (Floyd et al., 2016; Jansson et al., 2014). Meta-analysis of their findings (Fig. 7A) showed a significant reduction in stroke for metformin users (HR = 0.70, 95%CI 0.53–0.93, $p = 0.01$). The third study (Sullivan et al., 2011) compared metformin use to diabetics managing their diabetes through diet alone or with sulphonylurea, and found a non-significant increase in the incidence of stroke with metformin use in both cases.

Myocardial infarction incidence was examined in just two studies (Floyd et al., 2016; Jansson et al., 2014) and although (Jansson et al., 2014) showed a strong significant effect in favour of metformin, the result of the meta-analysis was a non-significant

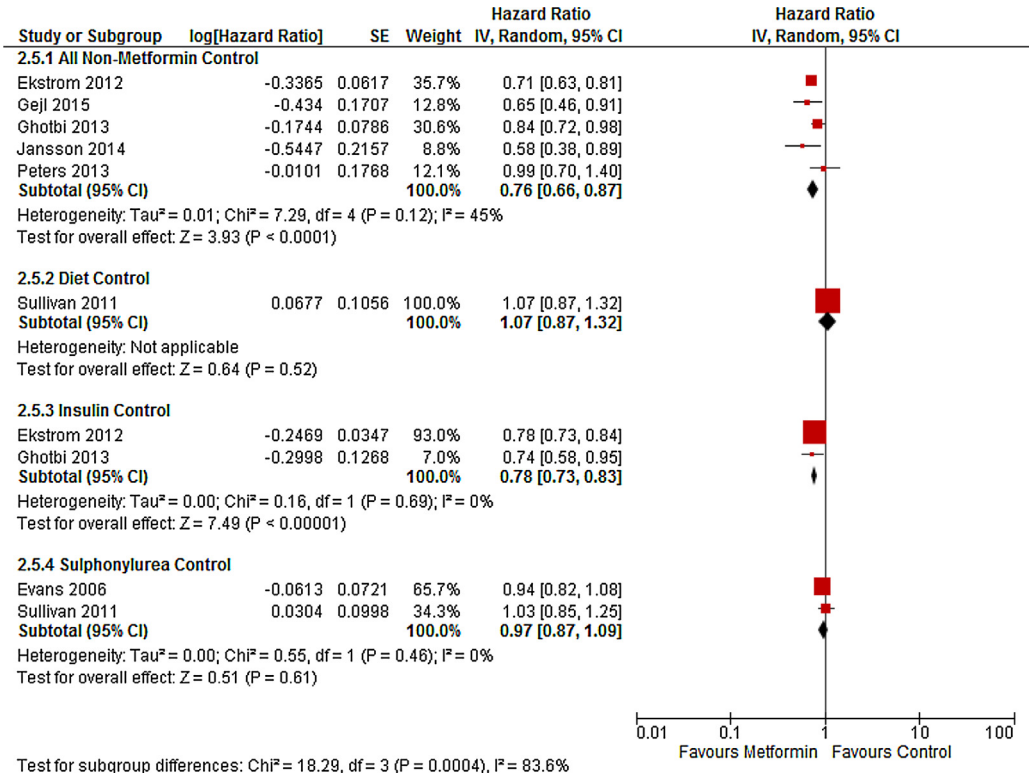

Fig. 6. Incidence of any CVD in diabetic patients treated with metformin compared to diabetic controls receiving other therapies. 2.5.1 'All Non-Metformin Control' includes studies where the controls were any diabetic patients who were not being treated with metformin (or controls who were receiving a broad range of therapies). 2.5.2'Diet Control' includes studies where controls were managing their diabetes though diet. 2.5.3 'Insulin Control' includes studies where controls were managing their diabetes using insulin 2.5.4 'Sulphonylurea control' includes studies where controls were managing their diabetes using sulphonylurea.

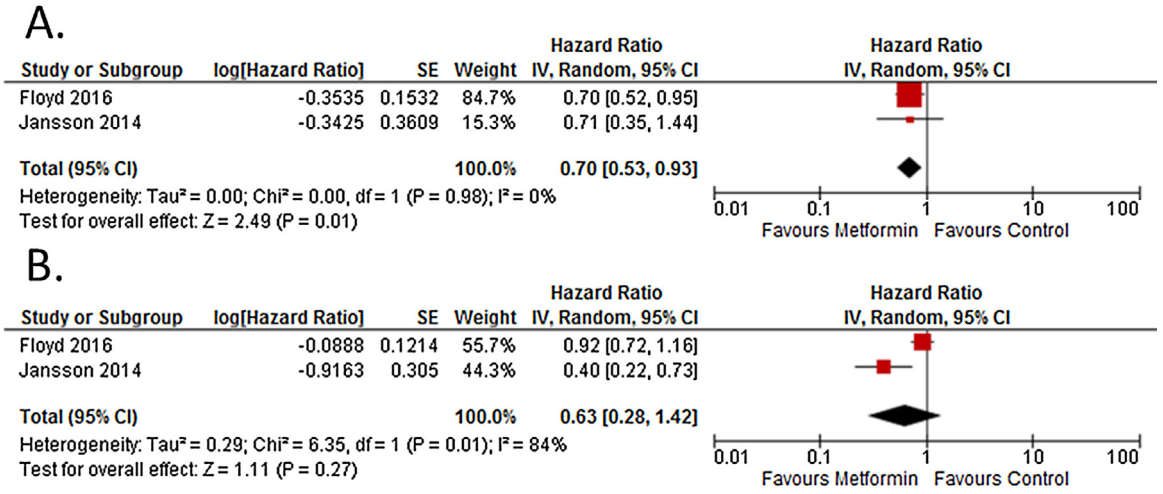

Fig. 7. A) Stroke incidence for diabetics taking metformin compared to diabetics not taking metformin. B) Myocardial infarction incidence for diabetics taking metformin compared to diabetics not taking metformin.

decrease in myocardial infarction for metformin users compared to diabetics not using metformin (Fig. 7B, HR = 0.63, 95%CI 0.28–1.42, p = 0.27).

Heart failure was investigated in four studies, however due to differences in study design and outcomes reported no meta-analysis could be performed. One study (Hartung et al., 2005) compared metformin users to other oral hypoglycaemic agent users with regards to hospitalisations resulting from heart failure, but found no significant effect. Another study (Koro et al., 2005) found non-significant increases for metformin on incidence of congestive heart failure compared to diabetics with no drug exposure and diabetics treated with sulphonylurea. Another study (Nichols et al., 2005) showed a non-significant decrease in congestive heart failure for diabetics treated with metformin compared to those treated with sulphonylurea. It also found a significant decrease in heart failure with metformin compared to insulin use (rate ratio = 0.39, 95%CI 0.19–0.80, p < 0.05). The final study (McAlister et al., 2008) compared the incidence of heart failure in metformin treated patients to those treated with sulphonylurea and found a non-significant decrease in heart failure for those receiving metformin.

Results for coronary heart disease also could not be meta-analysed. One study (Peters et al., 2013) found a non-significant reduction for users of metformin compared to other diabetics who were not receiving metformin, while another (Sullivan et al., 2011) found significant increases with metformin use compared to patients being treated with diet alone or sulphonylurea monotherapy. Other CVD outcomes investigated were left ventricular dysfunction, which was significantly more prevalent in diabetics being treated with metformin compared to those not taking metformin (OR = 1.62, 95%CI 1.09–2.40, p = 0.16) – although the authors of this cross-sectional study concluded that this outcome was likely due to confounding due to numerous large between group differences (Giorda et al., 2011) – and macrovascular morbidity and mortality (Kooy et al., 2009) which was significantly lowered by the addition of metformin to insulin therapy compared to the addition of a placebo to insulin therapy (HR = 0.34, 95%CI 0.21–0.56, p = 0.001).

3.2.3. Other diseases of ageing

Seven studies investigated the effect of metformin on diseases of ageing, other than cancer and CVD, although none could be combined in meta-analysis (Supp Table S3). Critical appraisal of studies (Supplementary material 2) showed differences between groups at baseline as well as short follow up with no reasons given for losses. Two studies compared outcomes for people using metformin to the general or non-diabetic population; neither reported on differences in ages, although one was a case-control study which matched for age (Geoghegan et al., 2004) and the other adjusted for age (Vestergaard et al., 2005). Amongst the five studies which compared people receiving metformin to those controlling their diabetes through other means there was heterogeneity in reporting; two studies included a cohort of metformin patients who were younger than their comparators (Hung et al., 2013; Masica et al., 2013), one reported that one subgroup of metformin users was younger and another older but did not report the overall comparison (Ng et al., 2014), one reported that metformin users were slightly older than patients assigned to a different medication (in an RCT design) (Kahn et al., 2008), and one did not report relative ages (Lin et al., 2015). All studies adjusted for age in their analyses with the exception of the RCT. Two studies investigated kidney failure or decline. One study (Hung et al., 2013) found a non-significant decrease for the incidence of a glomerular filtration event or end stage renal disease for diabetic patients treated with metformin compared to diabetic patients treated with sulphonylurea, however this decrease was significant in a subgroup of patients where urine protein at baseline was known and adjusted for (HR = 0.78, 95%CI 0.64–0.97). The same analyses were performed for patients treated with metformin in addition to sulphonylurea compared to sulphonylurea alone, however no significant differences were found. The second study found a non-significant reduction in the decline of estimated glomerular filtration rate to <60 ml/min/1.73 m^2 within one year for metformin users (Masica et al., 2013) compared to sulphonylurea users, however there was a significant reduction in risk of developing proteinuria (HR = 0.71, 95%CI 0.53–0.95, p < 0.05). These comparisons were repeated for treatment with thiazolidinediones compared to metformin, and no significant differences were found.

The effect of metformin on fracture risk was investigated in two studies. One study (Kahn et al., 2008) showed that metformin significantly decreased risk of fracture relative to treatment with rosiglitazone (HR = 0.64, 95%CI 0.46–0.88, p = 0.007). Stratified analysis showed that the effect persisted in women but not in men. The other study (Vestergaard et al., 2005) found the metformin users had lower risks of fracture compared to the general population for <150 defined daily doses (DDD) (OR = 0.87, 95%CI 0.86–0.96, p < 0.05), 150–499 DDD (OR = 0.81, 95%CI 0.71–0.94, p < 0.05), and ≥500 DDD (OR = 0.81, 95%CI 0.70–0.93, p < 0.05) consumed from the study start date to the date of censoring.

Additional studies on diseases of ageing investigated open angle glaucoma (Lin et al., 2015), which had a significantly lower incidence in diabetics taking metformin compared to other diabetics (HR = 0.75, 95%CI 0.59–0.95, p < 0.05), cognitive impairment (Ng et al., 2014), which was significantly less likely to develop in patients taking metformin compared to other diabetics (OR = 0.49, 95%CI 0.25–0.95, p < 0.05; a finding which remained significant in users who took metformin for more than 6 years before baseline (OR = 0.27, 95%CI 0.12–0.60, p < 0.05), but not those who took it for 6 years or less), and carpal tunnel syndrome (Geoghegan et al., 2004), which was not significantly associated with metformin use relative to the general population.

4. Discussion

This systematic review has shown through meta-analysis that diabetics taking metformin have a lower rate of all-cause mortality than non-diabetic people and the general population. Our results suggest that metformin could be an effective intervention to extend the lifespans of people who do not have diabetes. This is supported by additional meta-analyses showing that diabetics taking metformin had lower rates of all-cause mortality than diabetics receiving other therapies after adjusting for relative disease control. This was true for metformin compared to diabetics receiving any non-metformin therapy, insulin, or sulphonylurea, however, the result was non-significant for diet therapy. This finding could be due to diet therapy being a more likely option for people with early or less severe diabetes, or it could alternatively be explained by improved diet and lifestyle having an effect beyond disease control comparable to metformin. With only two studies contributing to the meta-analysis further research is needed for conclusions to be drawn.

Other results suggest that metformin's effect on all-cause mortality could be due to it having a geroprotective effect of delaying or preventing diseases of ageing, particularly cancer and CVD which are two of the leading causes of death and disability worldwide (Mathers and Loncar, 2006). We show that diabetic people taking metformin had a lower rate of developing any cancer compared with the general population, and had a lower risk of developing colorectal, breast or lung cancer compared with diabetics managing their diabetes through non-metformin therapies after adjusting for disease control. The rate of any form of CVD was similarly lower for diabetic people taking metformin compared to those managing their diabetes through any non-metformin therapy or insulin therapy after adjusting for disease control, however findings for sulphonylurea were non-significant. The incidence of stroke was also reduced with metformin use compared to any non-metformin therapy; however there was no significant effect for metformin on myocardial infarction.

These findings rest on the credibility of two assumptions: that improvements in survival and reduced onset of diseases of ageing seen in diabetics above the outcomes of people who do not have diabetes can be generalised to the non-diabetic population, and that benefits seen between populations receiving different therapies for diabetes (which are still present after adjusting for disease control) are independent on the therapies' effects on diabetes and are likewise generalisable. Of the two, the former is the more robust assumption, although the potential for confounding, as with any observational research, does exist. As such, the findings for all-cause mortality and cancer – which are backed by comparisons to the non-diabetic population – should be considered more reliable than those for CVD – which are based solely on comparisons to diabetics treated with other therapies. However, taken together

these results provide strong evidence, from a combined population of 417,316 for all-cause mortality compared to the non-diabetic or general population alone, to support the hypothesis that metformin has a geroprotective effect in humans, slowing the progression of diseases of ageing and in doing so extending both health and lifespans.

Beyond the assumptions discussed, limitations of this research include that none of the meta-analyses included sufficient studies for any investigation of publication bias, study designs were entirely observational (with two exceptions that showed benefits for metformin on fracture (Kahn et al., 2008) and macrovascular morbidity and mortality (Kooy et al., 2009)), and none of the data for diseases of ageing beyond cancer and CVD could be combined through meta-analysis despite promising findings for kidney failure, fracture risk, open angle glaucoma and cognitive impairment. With regards to cognitive impairment, in the conduct of this review's search, numerous additional studies were found which investigated the effect of metformin on measures of dementia. However, these studies were not eligible for inclusion due to investigating average level of cognitive ability (rather than the incidence or prevalence of impairment) or not adjusting for disease control. An additional systematic review with broader inclusion criteria relating to dementia outcomes is now planned (Campbell et al., 2017). Diabetes, despite being a major chronic disease which becomes progressively more common with age, was not investigated by this review as metformin being an intervention for diabetes was too much of a complicating factor. However, experimental studies have directly investigated the effect of prophylactic metformin for the prevention of diabetes (in high BMI populations) and shown that it significantly reduced its development (Andreadis et al., 2009; Knowler et al., 2009).

The primary issue with study quality in this systematic review, highlighted by critical appraisal, was that studies rarely compared groups that did not have meaningful differences at the beginning of the observation period. Where diabetics receiving metformin were compared to general or non-diabetic populations, this aspect is essentially a feature of the study design. However, for metformin compared to other diabetic therapies it is more concerning, as it reflects a trend for people receiving metformin to be younger with shorter durations of disease, which has the potential to bias results towards finding a protective effect for metformin. Critical appraisal also showed that studies were generally thorough in adjusting for potential confounding factors, however, and a sizeable proportion of studies utilised matching. As such, the potential impact of this source of bias is at least mitigated. Additionally, the general pattern of findings for metformin compared to other diabetic therapies being reproduced by findings for metformin compared to the general or non-diabetic population suggests that they are real and not the result of confounding. Studies frequently had follow up periods less than five years, which affects the likelihood of age related outcomes having an opportunity to occur, however the use of summary measures which incorporate time (i.e. hazard and rate ratios) will have accommodated this. Finally, studies did not report on reasons for (or the existence of) loss to follow up which, if known, may have revealed or precluded potential sources of bias.

Future research in this area should include controlled trials. Two existing trials on the effects of metformin on ageing – Metformin in Longevity Study (MILES NCT02432287) and Targeting Ageing with Metformin (TAME) (Barzilai et al., 2016) – are currently planned. The findings of this systematic review suggest that studies on the effect of metformin in older people on the incidence of chronic diseases (healthspan) and longevity (lifespan) over the long term are warranted. It must be stressed, however, that any immediate use of metformin as an intervention for ageing by the general population is not supported. Despite being a relatively safe drug, with feared effects on lactic acidosis and kidney function emerging to be minor (Ekstrom et al., 2012; Vasisht et al., 2010), metformin is not risk free. Although studies in mice have generally been positive, some have shown increased mortality when taken at higher concentrations (Martin-Montalvo et al., 2013), and others have suggested that its effects may be gender exclusive (favouring females (Anisimov et al., 2010b)), an observation which is supported by some subgroup analyses performed in included studies (Bodmer et al., 2012b; Kahn et al., 2008). As such, there is a risk that people taking metformin as a geroprotective agent will experience harm or no effect even if it is ultimately found to be beneficial in some circumstances. Additionally, recent work by Wang et al. – who showed in an included study that the presence of frailty significantly attenuated the effect of metformin on mortality (Wang et al., 2014) –found that older men's propensity for diseases of ageing significantly interacted with metformin's effect on the development of these diseases (Wang et al., 2017).

The findings reported in this systematic review remain preliminary generalisations, primarily making use of existing observational evidence collected for other purposes to investigate the credibility of the hypothesis that the insulin sensitiser metformin may extend the health and lifespans of people from the non-diabetic population. Differences in baseline characteristics were found which had the potential to bias results both towards positive findings (where metformin users were compared to other diabetics) as well as away from (where metformin users were compared to non-diabetics). While they should not be overstated, the apparent association with reductions in all-cause mortality and diseases of ageing found through meta-analysis do support this hypothesis, and metformin should be investigated as an intervention for ageing in future clinical trials.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arr.2017.08.003.

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