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Glucagon-like peptide-1 receptor agonists improve biomarkers of inflammation and oxidative stress: A systematic review and meta-analysis of randomised controlled trials

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Abstract

Aim: To conduct a meta-analysis and systematic review to examine the effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on clinical biomarkers of inflammation and oxidative stress in patients with type 2 diabetes.

Methods: Medline, Embase and the Cochrane Library were searched for randomised controlled trials (RCTs) that examined changes with GLP-1RAs in a priori selected biomarkers of inflammation: C-reactive protein (CRP), adiponectin, tumour necrosis factor-alpha (TNFα), plasminogen activator inhibitor-1, interleukin-6, leptin; and of oxidative stress: malondialdehyde (MDA); 8-iso-prostaglandin F2α; and 8-hydroxy-2′-deoxyguanosine (8-OHdG).

Results: We included 40 eligible RCTs (n = 6749) with a median follow-up of 6 months, a mean participant age of 53.1 years, 56.3% females, glycated haemoglobin (HbA1c) 55.6 mmol/mol, body mass index 28.8 kg/m^2 and diabetes duration 7.46 years. Analysis of GLP-1RAs versus standard diabetes therapies or placebo revealed significant reductions in CRP, TNFα and MDA, and significant increases in adiponectin for (mean difference −0.54 mg/L [−0.75, −0.34]; standard mean difference [SMD] −0.39 [−0.62, −0.15]; SMD −0.84 [−1.61, −0.06] and SMD 0.30 [0.12, 0.49], respectively [95% confidence intervals]). Systolic blood pressure decreased significantly and was significantly and strongly correlated with a reduction in CRP. Homeostatic model assessment of insulin resistance was also significantly correlated with a reduction in CRP, but HbA1c was not.

Conclusions: There is strong evidence supporting clinically relevant anti-inflammatory and antioxidant effects of GLP-1RAs. This may be used to guide future targeted clinical use of GLP-1RAs and the development of medications seeking to target the cardioprotective properties of GLP-1RAs.

* Jonathan J. H. Bray and Harri Foster-Davies are co-first authors.

KEYWORDS
glucagon-like peptide-1 receptor agonists, inflammation, oxidative stress, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) leads to significant macro- and microvascular complications. T2DM is associated with a doubling in the risk of cardiovascular complications[1] and is the leading cause of chronic kidney disease worldwide.[2] There is evidence to implicate inflammation and oxidative stress in the pathogenesis of T2DM and associated cardiovascular and renal complications. Furthermore, acute phase reactants and proinflammatory cytokines, such as C-reactive protein (CRP) and interleukin-6 (IL-6) predict the development of T2DM in addition to the risk of complications.[3,4] Elevated circulating concentrations of inflammatory biomarkers are consistently found in people with T2DM.[5,6] Indeed, cardiovascular events in individuals with T2DM are associated with raised CRP and are inversely related to adiponectin levels.[7–9] Similarly, concentrations of 8-iso-prostaglandin F2α (8-iso-PGF2α), malondialdehyde (MDA), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) biomarkers have been found to be elevated in patients with T2DM compared to healthy controls in both serum[10–12] and urine.[13–15] Furthermore, within T2DM cohorts, higher levels of oxidative stress biomarkers are associated with increased cardiovascular[15] and renal disease risk.[16] Additional data also support a role for inflammation and oxidative stress in the pathogenesis of nonalcoholic fatty liver disease (NAFLD), which affects over two-thirds of those with T2DM.[17] Serum levels of adiponectin are low in patients with T2DM presenting with liver disease,[18] and the severity of liver disease appears to be correlated with inflammatory biomarkers such as tumour necrosis factor-alpha (TNFα)[19] and IL-6.[20] Markers of oxidative stress are also higher in T2DM patients with nonalcoholic steatohepatitis as compared with T2DM patients without liver disease.[21]

During the past decade, studies have suggested that glucagon-like peptide-1 receptor agonists (GLP-1RAs) exhibit cardiorenal protective properties. Major cardiovascular trials in patients with T2DM, including the LEADER, SUSTAIN-6, HARMONY Outcomes and REWIND trials,[22–25] have collectively demonstrated a significant reduction in cardiovascular death with GLP-1RA therapy, ranging from 12% to 26%. The LEADER and REWIND trials also report a greater than 20% reduction in the risk of developing new macroalbuminuria, along with favourable trends in other clinically relevant adverse renal outcomes.[26,27] Sodium-glucose cotransporter-2 (SGLT2) inhibitors have similar cardiorenal protective properties and we have recently described that SGLT2 inhibitors reduce biomarkers of inflammation and oxidative stress.[28] Although a number of mechanisms have been proposed, it is unclear how GLP-1RAs exert their cardiorenal protective effects in patients with T2DM and whether an impact on inflammation and oxidative stress may contribute. This meta-analysis and systematic review of randomised trials aims to examine the effect of GLP-1RAs on inflammatory and oxidative stress biomarkers in clinical practice.

2 | METHODS

This review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered with PROSPERO (CRD42020182116).

2.1 | Search strategy

We searched Medline, Embase, and the Cochrane Library up to April 2020 using the following search terms limited to humans: (glucagon-like peptide-1 receptor agonist OR ([GLP1 OR GLP-1] AND [receptor agonist OR analog*]) OR GLP 1RA* OR GLP 1 RA* OR incretin mimetic* OR specific drug names) AND (C-reactive protein OR adiponectin OR leptin OR interleukin 6 OR tumour necrosis factor-alpha OR vascular cell adhesion protein/ oxidative stress). The detailed search strategy is provided in Tables S1A and S1B, and is available on PROSPERO. Medical Subject Heading terms were used in most cases. Following the search and removal of duplicates, two reviewers screened titles (J.J.H.B. and H.F.D.) and abstracts for relevance, before assessing full texts for inclusion eligibility (Figure 1).

2.2 | Study selection

Only prospective randomised controlled trials (RCTs) were included, of either parallel or crossover design. Observational studies and articles without original data in human participants were excluded. Our study population of interest was adults with impaired glucose tolerance (prediabetes and type 2 diabetes mellitus). We excluded studies that included participants aged less than 18 years or with type 1 diabetes mellitus. Only studies with biomarker outcomes that could be compared through meta-analysis or
control-subtracted mean were included. Despite having very similar results, Fan et al,[30] 2013 and Tian et al,[31] 2018 were considered different studies as they were conducted in different Chinese hospitals and had different baseline characteristics.

2.3 | Outcomes of interest and comparisons

Our biomarkers of interest were selected a priori and included, for inflammation: CRP, adiponectin, leptin, IL-6, TNFα, vascular cell

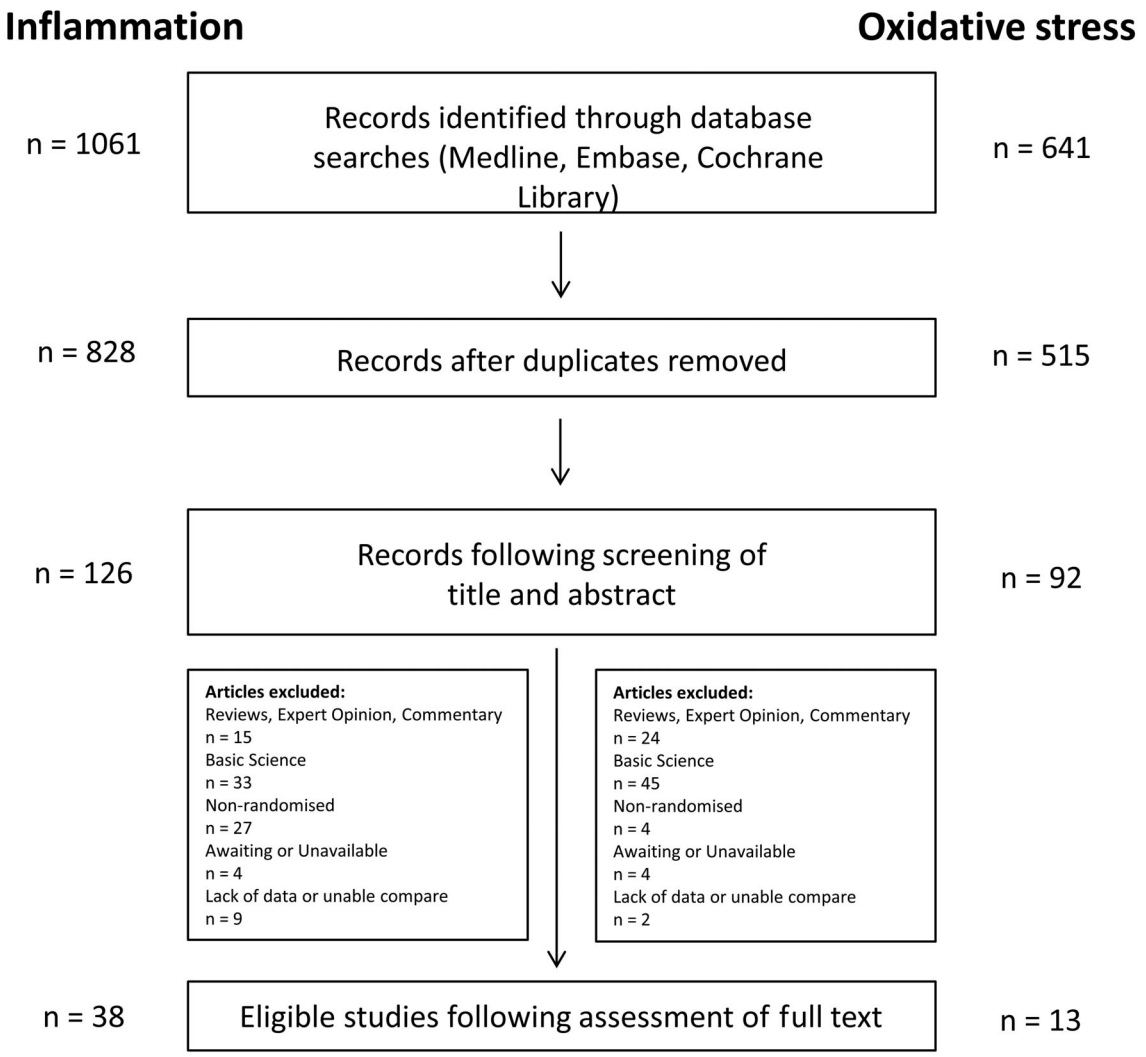

FIGURE 1 Flow diagram based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist[29] showing resulting articles found and reasons for exclusion

adhesion protein-1 (VCAM1) and plasminogen activator inhibitor-1 (PAI-1), and for oxidative stress: 8-iso-PGF2α, 8-OHdG, oxidised low-density lipoprotein (ox-LDL) and MDA. These were selected as they are widely accepted and reported biomarkers, with clear significance and validity.

For each biomarker, comparisons were made between study arms exposed to GLP-1RAs and control therapies. Subgroup analysis was undertaken to compare GLP-1RAs with (a) placebo, (b) diabetes medications and (c) insulin. Comparison of GLP-1RAs versus all three subgroups is referred to as 'Total'. VCAM1 and ox-LDL were excluded due to insufficient data.

2.4 | Data extraction and synthesis

Three reviewers (J.J.H.B., H.F.D. and A.L.H.) independently transferred raw data from selected papers into preformatted tables. Continuous outcomes were converted into equivalent units for each biomarker. Patient characteristics were obtained and are shown in Table 1. Follow-up data for GLP-1RA-exposed and control groups were taken in combination with standard deviations (SDs) and used to construct forest plots for the following biomarkers: CRP (Figure 2A); adiponectin (Figure 2B); TNFα (Figure 2C); IL-6 (Figure 2D); leptin (Figure 2E); PAI-1 (Figure 2F); serum MDA (Figure 2G); serum 8-iso-PGF2a (Figure 2H), and urinary 8-OHdG (Figure 2I). In order to analyse the comparison of change from baseline to follow-up between GLP-1RAs and control groups, we produced control-subtracted change from baseline values. To allow for differences in measurement techniques, these control-subtracted change data were converted to control-subtracted percentage change from GLP-1RAs at baseline (Table S4). Control-subtracted mean change statistics were analysed in conjunction with *P* values from statistical tests comparing GLP-1RAs at baseline and follow-up, and where this was not available between GLP-1RAs and control.

TABLE 1 Summary of reported patient characteristics

Study (first author, date)	Number randomised, n	Study duration	Population (eg, country)	Inclusion criteria	Study arms	Mean ±SD age, years	Sex split, % male	HbA1c, mmol/mol	BMI, kg/m^2	Mean or median diabetes duration, years
Wang 2020[32]	60	6 mo	China	T2DM, post-stroke	Sitagliptin	66.1 (5.9)	56.7	73.3 (26.8)	25.7 (4.28)	8.99 (2.65)
					Liraglutide	67.2 (7.10)	46.7	70.1 (27.5)	25.8 (3.76)	8.19 (3.05)
Yao 2020[33]	65	2 wk	China	T2DM	Metformin	49.0 (42.5, 61.0)	90.0	85.8 (72.7, 108)	29.0 (4.20)	6.00 (3.00, 13.0)
					Liraglutide + metformin	50 (42.5, 63.5)	76.7	78.1 (69.4, 119)	29.4 (3.40)	9.00 (2.00, 17.5)
Ahmadi 2019[34]	124	24 wk	Sweden	T2DM, BMI 27.5-45	Placebo	63.6 (7.70)	66.1	74.4 (11.7)	33.5 (4.00)	17.0 (8.20)
					Liraglutide	63.8 (8.20)	63.5	74.6 (8.38)	33.7 (4.30)	17.3 (7.70)
Anholm 2019[35]	41	26 wk	Sweden	New T2DM, stable CAD, BMI ≥25	Metformin	62.3 (7.60)	79.0	46.4 (4.23)	31.6 (4.80)	<2.00
					Liraglutide					
Hartman 2019[36]	105	26 wk	United States	T2DM, BMI 23-45	Placebo	56.6 (8.90)	57.0	63.9 (7.62)	32.4 (6.00)	8.6 (7.00)
					Dulaglutide	58.7 (7.8)	44.0	65.0 (8.46)	32.4 (5.40)	9.30 (7.10)
Li 2019a[37]	23	26 wk	China	T2DM, BMI 19-35	Glimepride	55.3 (6.60)	60.0	63.0 (8.29)	24.8 (2.64)	2.00 (1.00, 3.50)
					Dulaglutide	54.8 (5.33)	53.8	68.1 (7.87)	24.0 (2.50)	2.00 (0.50, 9.00)
Li 2019b[38]	60	2 wk	China	New T2DM, BMI 25-35	Insulin	46.0 (42.5, 59.0)	90.0	98.9 (78.1, 116)	29.7 (26.3, 30.0)	-
					Insulin + Liraglutide	50.0 (42.4, 66.0)	76.7	90.2 (89.1, 105)	27.3 (25.9, 28.7)	-
Liu 2019[39]	92	12 wk	China	T2DM	Insulin	56.4 (4.15)	54.4	-	-	9.85 (1.34)
					Insulin + Liraglutide					
Pavithra 2019[40]	80	26 wk	India	T2DM ±complications	Metformin + Sitagliptin	47.6 (4.70)	65.0	-	-	7.10 (2.00)
					Metformin + Liraglutide	43.2 (6.20)	49.0	-	-	6.40 (2.70)
Wang 2019[41]	25	52 wk	China	T2DM, BMI 19-35, stable weight	Insulin	65.4 (11.1)	55.6	71.9 (5.42)	24.6 (2.12)	5.00 (3.00, 11.5)
					Dulaglutide	59.9 (8.17)	62.5	71.0 (13.3)	25.2 (2.67)	8.00 (5.00, 14.5)
Lambadiari 2018[42]	60	26 wk	Greece	Treatment-naïve T2DM	Metformin	50.0 (12.0)	66.7	68.3 (10.2)	27.7 (2.00)	-
					Liraglutide	51.0 (10.0)	66.7	70.5 (16.9)	32.9 (5.00)	-
Tian 2018[31]	129	12 wk	China	T2DM, NAFLD	Metformin	56.4 (8.40)	57.0	64.9 (4.99)	27.6 (1.77)	-
					Liraglutide	58.5 (7.60)	59.6	65.5 (4.32)	28.2 (1.86)	-
Wagner 2019[43]	224	6 mo	Spain	T2DM	Placebo	52.6 (13.8)	33.3	66.1 (55.2, 81.4)	35.0 (6.20)	7.42 (4.10)
					Liraglutide	53.2 (9.70)	41.7			10.0 (7.20)

TABLE 1 (Continued)

Study (first author, date)	Number randomised, n	Study duration	Population (eg, country)	Inclusion criteria	Study arms	Mean ±SD age, years	Sex split, % male	HbA1c, mmol/mol	BMI, kg/m^2	Mean or median diabetes duration, years
Zhang 2018[44]	60	8 wk	China	Treatment-naïve T2DM, 18-40 y-of-age, BMI 25-35	Metformin	-	-	-	-	-
					Liraglutide	-	-	-	-	-
Bouchi 2017[45]	19	36 wk	Japan	Insulin-treated T2DM, BMI ≥25	Insulin	60.0 (22.0)	33.0	62.8 (5.92)	28.2 (2.50)	-
					Lirtaglutide	57.0 (16.0)	63.0	66.1 (4.23)	27.7 (2.50)	-
Le Roux 2017[46]	2254	160 wk	27 countries	Prediabetes/ T2DM, BMI ≥30, stable weight, ±dyslipidaemia, ±HTN	Placebo	47.3 (1.80)	23.0	38.8 (2.54)	-	-
					Liraglutide	47.5 (11.7)	24.0	39.9 (2.54)	-	-
Liu 2017[47]	60	24 wk	China	T2DM, CAD	Metformin	59.0 (17.0)	46.7	76.0 (9.31)	29.6 (1.75)	7.00 (4.00)
					Liraglutide	58.0 (15.0)	53.3	74.9 (11.0)	29.6 (1.68)	8.00 (5.00)
					Metformin + Liraglutide	57.0 (14.0)	46.7	79.2 (10.2)	29.7 (1.78)	9.00 (6.00)
					Liraglutide	58.0 (16.0)	53.3	78.1 (11.0)	29.8 (1.85)	8.00 (5.00)
Quan 2017[48]	200	12 wk	China	New T2DM, BMI 24-40, stable weight	Metformin	57.4 (9.20)	41.0	72.7 (11.0)	28.1 (2.10)	0.70 (0.50)
					Exenatide	58.1 (10.2)	40.0	70.5 (10.2)	27.3 (2.40)	0.80 (0.40)
Santilli 2017[49]	62	65 wk	Italy	IGT/IFG/T2DM, BMI <30	Metformin	52.2 (50.2, 57.2)	50.0	43.2 (37.7, 47.5)	35.0 (31.3, 40.3)	-
					Liraglutide	55.5 (48.2, 63.7)	55.0	41.5 (37.9, 49.7)	36.7 (34.7, 40.9)	-
Von Scholten 2017[50]	32	12 wk	Denmark	T2DM, albuminuria	Placebo	65.0 (7.00)	81.0	60.7 (9.31)	-	15.0 (7.00)
					Liraglutide					
Dutour 2016[51]	44	26 wk	France	T2DM, BMI ≥30, stable weight	Placebo	52.0 (2.00)	36.0	-	35.0 (1.20)	4.00 (1.00, 10.0)
					Exenatide	51.0 (2.00)	59.0	-	37.2 (1.80)	4.00 (2.00, 8.00)
Farr 2016[52]	20	17 d	United States	T2DM	Placebo	49.7 (2.40)	55.0	-	31.2 (1.70)	-
					Liraglutide	49.7 (2.40)	55.0	-	31.9 (1.70)	-
Probstfield 2016[53]	102	26 wk	United States	T2DM >12 mo, insulin dependent >3 mo, 40-75 y-of-age, CVD or increased risk of CVD, BMI ≤45	Insulin	62.0	63.0	62.8	34.0	15.0
					Exenatide + insulin					

(Continues)

TABLE 1 (Continued)

Study (first author, date)	Number randomised, n	Study duration	Population (eg, country)	Inclusion criteria	Study arms	Mean ±SD age, years	Sex split, % male	HbA1c, mmol/mol	BMI, kg/m^2	Mean or median diabetes duration, years
Savvidou 2016[54]	110	26 wk	Greece	Insulin-dependent T2DM	Insulin	63.7 (7.10)	33.3	63.9 (7.62)	33.4 (3.90)	-
					Exenatide	62.2 (7.20)	45.5	67.2 (12.7)	32.2 (5.50)	-
Takeshita 2015[55]	122	12 wk	Japan	T2DM, 20-80 y-of-age	Vildagliptin	64.7 (12.4)	62.0	65.0 (10.2)	24.5 (4.60)	-
					Liraglutide		64.8	63.9 (7.62)	25.4 (4.80)	-
Bi 2014[56]	33	6 mo	China	T2DM	Insulin	53.5 (2.40)	45.5	76.0 (2.54)	24.5 (0.60)	-
					Pioglitazone	51.0 (2.20)	36.4	67.2 (3.39)	23.9 (1.00)	-
					Exenatide	50.8 (4.00)	63.6	70.5 (3.39)	25.1 (1.10)	-
Suzuki 2014[57]	56	26 wk	Japan	Treatment naïve T2DM	Sitagliptin	56.1 (15.3)	56.3	76.0 (13.5)	26.3 (7.20)	1.90 (2.30)
					Liraglutide	58.6 (15.9)	62.5	83.6 (18.6)	28.2 (7.20)	2.40 (2.80)
Hu 2013[58]	30	16 wk	China	Treatment naïve T2DM, BMI 20-40	Placebo	-	-	69.3 (5.84)	23.9 (3.82)	-
					Liraglutide	-	-	73.1 (10.2)	23.8 (3.75)	-
Fan 2013[30]	117	12 wk	China	Poorly controlled T2DM without complications, NAFLD	Metformin	54.7 (12.1)	55.9	64.9 (4.99)	27.6 (1.77)	-
					Exenatide	51.0 (10.1)	57.1	65.5 (4.32)	28.2 (1.86)	-
Kelly 2012[59]	50	12 weeks	United States	Prediabetes	Metformin	58.1 (10.1)	28.0	-	35.8 (7.00)	-
					Exenatide	58.7 (10.0)	20.0	-	35.3 (5.50)	-
Forst 2012[60]	44	6 wk	Germany	T2DM	Metformin	57.9 (5.90)	52.6	46.0 (3.13)	33.0 (5.00)	4.80 (3.20)
					Liraglutide + metformin	55.1 (6.20)	47.6	45.6 (3.13)	33.0 (7.00)	3.80 (3.00)
Henry 2012[61]	326	24 wk	United States	T2DM, BMI 25-45, stable weight	Placebo	54.3 (9.60)	50.0	65.0 (7.62)	32.0 (5.30)	7.5 (5.80)
					Taspoglutide 10 mg	52.5 (10.3)	59.0	66.1 (8.46)	32.8 (5.30)	7.30 (4.60)
					Taspoglutide 20 mg	55.5 (10.1)	53.0	65.0 (7.62)	33.0 (5.0)	8.30 (5.30)
Derosa 2012[62]	171	12 mo	Italy	Poorly controlled, treatment naïve T2DM, BMI 25-30	Placebo	56.7 (7.30)	48.2	62.8 (5.08)	31.7 (1.50)	7.80 (3.10)
					Exenatide	57.3 (7.70)	50.6	65.0 (6.77)	31.9 (1.70)	7.60 (2.80)
Sathyanarayana 2012[63]	21	52 wk	United States	T2DM without complications, 30-70 y-of-age, stable weight	Pioglitazone	52.0 (3.00)	-	67.2 (3.39)	29.7 (0.90)	-
					Pioglitazone + Exenatide	52.0 (3.00)	-	65.0 (4.23)	34.1 (1.30)	-

TABLE 1 (Continued)

Study (first author, date)	Number randomised, n	Study duration	Population (eg, country)	Inclusion criteria	Study arms	Mean ±SD age, years	Sex split, % male	HbA1c, mmol/mol	BMI, kg/m^2	Mean or median diabetes duration, years
Simo 2012[64]	1029	156 wk	14 countries	T2DM, BMI 25-40, stable weight	Glimepiride	57.0 (9.00)	52.0	57.4 (5.92)	32.2 (4.00)	-
					Exenatide	56.0 (10.0)	56.0	58.5 (5.92)	32.5 (4.20)	-
Wu 2011[65]	23	16 wk	China	T2DM	Placebo	54.0 (95.0)	27.0	61.7 (7.62)	26.3 (3.00)	5.00 (2.50)
					Exenatide	57.0 (10.0)	50.0	60.7 (5.08)	26.3 (1.90)	7.30 (4.40)
Bunck 2010[66]	69	51 wk	Finland, Sweden and the Netherlands	T2DM	Insulin	58.3 (1.30)	66.7	57.4 (0.85)	30.1 (0.60)	4.00 (0.60)
					Exenatide	58.4 (1.40)	63.9	59.6 (0.85)	30.9 (0.70)	5.70 (0.80)
Derosa 2010[67]	128	52 wk	Italy	Poorly controlled T2DM, BMI 25-30	Glibenclamide	56.0 (7.00)	50.8	73.8 (6.77)	28.5 (1.40)	-
					Exenatide	57.0 (8.00)	47.6	72.7 (5.92)	28.7 (1.50)	-
Wysham 2010[68]	514	52 wk	United States	T2DM, BMI 25-45	Placebo + sitagliptin	53.0 (11.0)	58.0	69.4 (9.31)	32.0 (5.00)	6.00 (5.00)
					Placebo + pioglitazone	53.0 (10.0)	51.0	68.3 (8.46)	32.0 (5.0)	6.00 (5.00)
					Placebo + exenatide	52.0 (10.0)	57.0	70.5 (10.2)	32.0 (5.00)	6.00 (5.00)
Courreges 2008[69]	165	14 wk	Denmark	T2DM	Placebo	-	-	65.0-69.4	28.9-31.2	-
					Liraglutide 0.65 mg					
					Liraglutide 1.25 mg					
					Liraglutide 1.9 mg					

Note: Values are given as mean (SD) or where not available median (interquartile range [Q1, Q3]) or range (min-max). All studies only included adults.
Abbreviations: BMI, body mass index (kg/m^2); CAD, coronary artery disease; CVD, cardiovascular disease; HTN, hypertension; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; y-of-age, years-of-age.

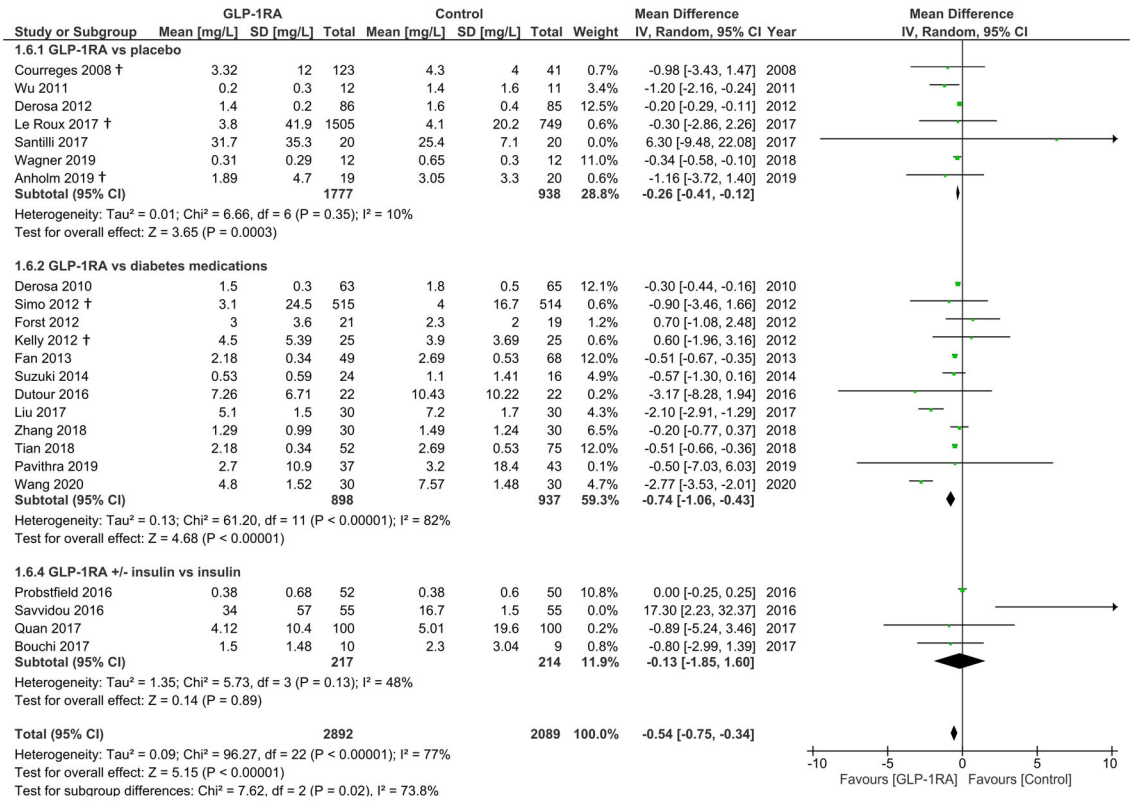

FIGURE 2 Forest plots showing the effect of glucagon-like peptide-1 receptor agonists (GLP-1RAs) compared to other diabetes therapy (Total), and subgroup comparisons: GLP-1RA versus (A) placebo, (B) diabetes medications, and (C) insulin. The following biomarkers are shown: (A) C-reactive protein, (B) adiponectin, (C) tumour necrosis factor α, (D) plasminogen activator inhibitor-1, (E) leptin, (F) interleukin-6, (G) serum 8-iso-prostaglandin F2α (8-iso-PGF2α), (H), malondialdehyde, (I) urinary 8-hydroxy-2′-deoxyguanosine. †Imputed values[70]

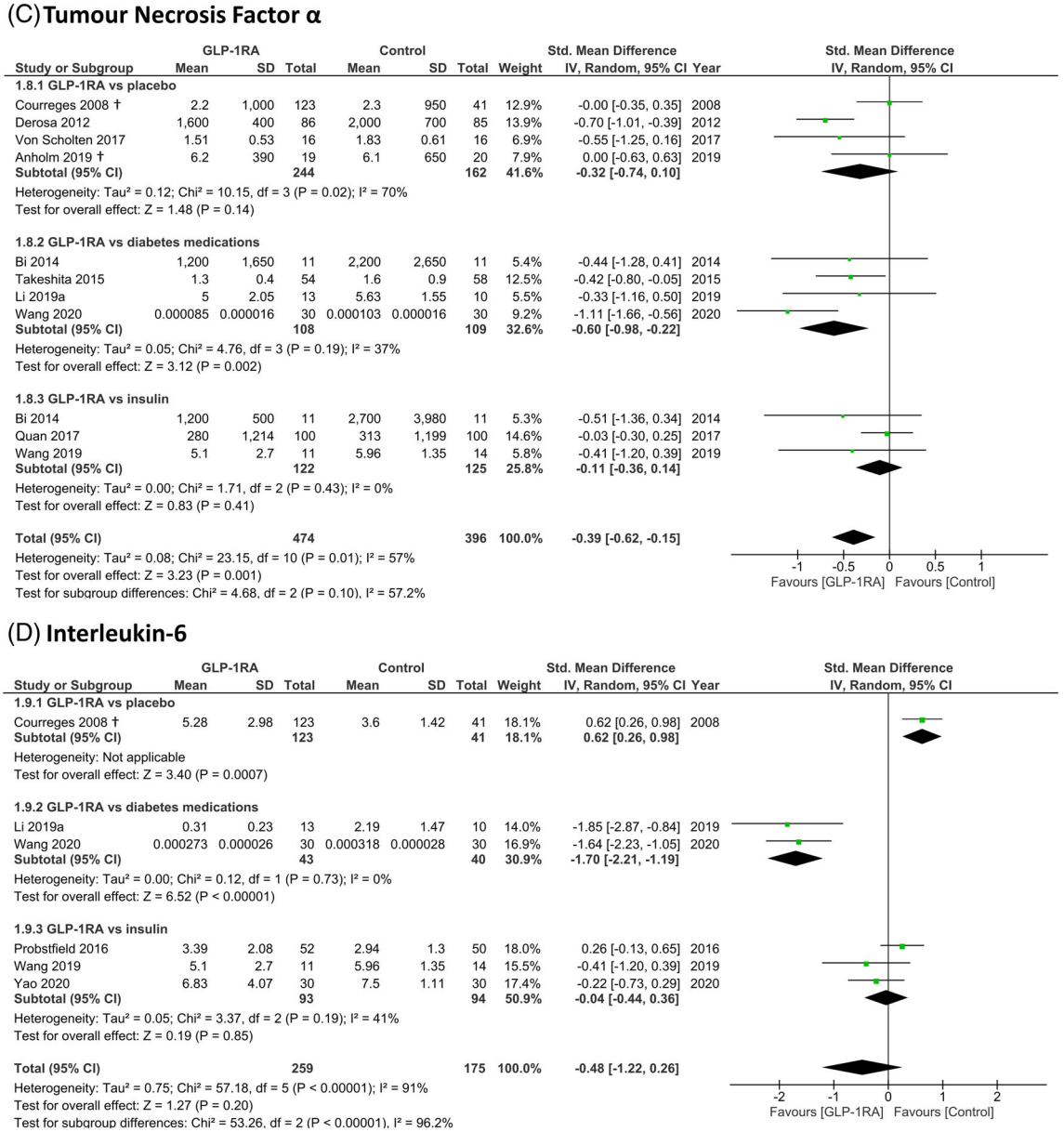

FIGURE 2 (Continued)

2.5 | Associations with biomarker changes and other clinically relevant outcomes

Raw data were collected on other clinically relevant variables to examine whether changes in biomarkers were associated with changes in clinically meaningful variables. In this respect, control-subtracted percentage changes were produced to compare proportional changes in the following variables with relevant biomarkers: body weight, body mass index (BMI), glycated haemoglobin (HbA1c), fasting glucose, 120-minute postprandial glucose, homeostatic model assessment of insulin resistance (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, total cholesterol, alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase (GGT), albumin/creatinine ratio (ACR), creatinine (Cr) and the echocardiographic ratio of early to late ventricular filling velocities (E/A ratio).

2.6 | Quality and risk-of-bias assessment

The Cochrane risk-of-bias tool for randomised trials (RoB 2) tool was used to assess for risk of bias.[71] To determine the degree of confidence in the effect of GLP-1RAs on our biomarkers of interest we used the Grading of Recommendations Assessment, Development and Evaluation (GRADEpro) tool.[72]

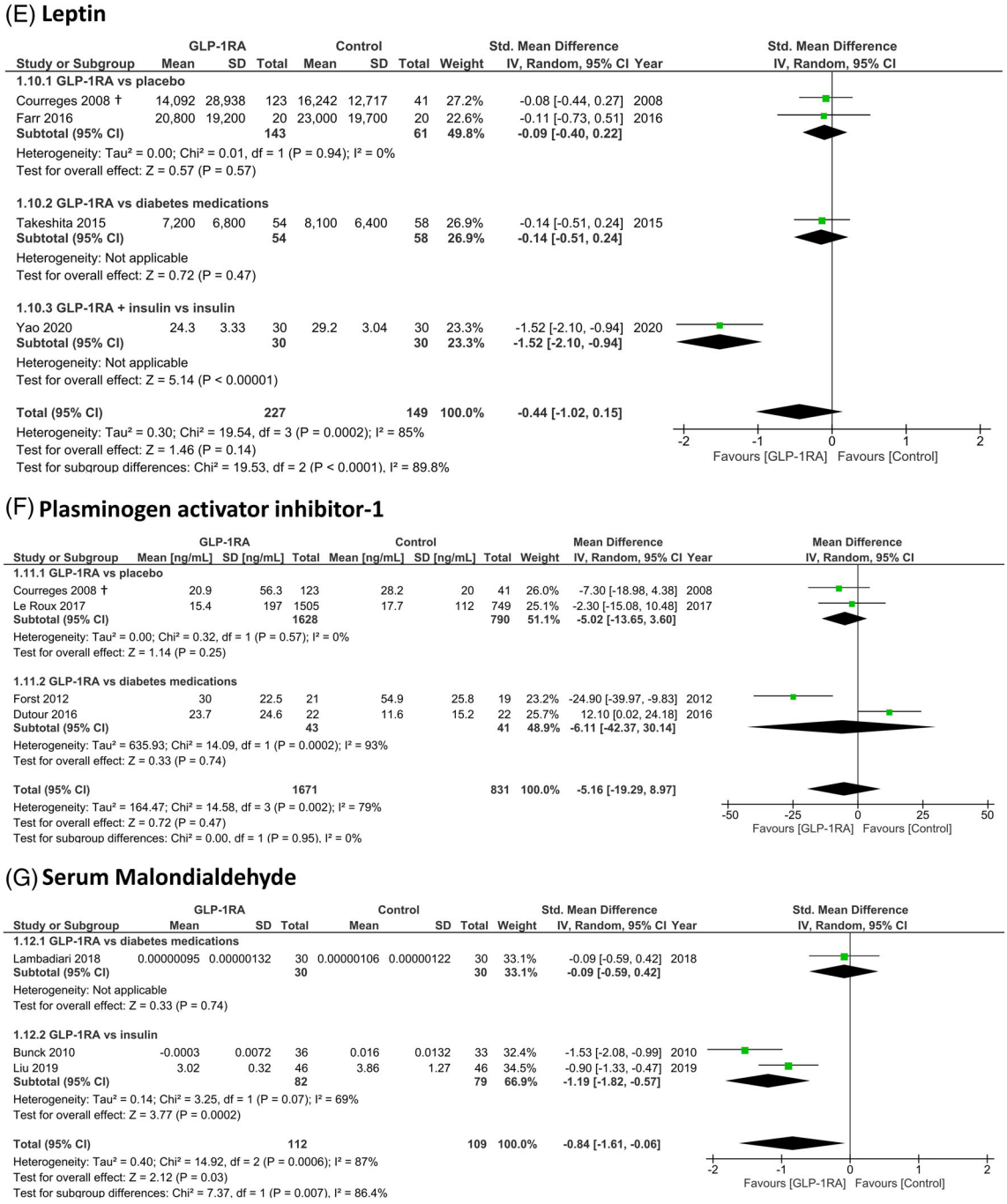

FIGURE 2 (Continued)

2.7 | Statistical analysis

Participant characteristics are presented as weighted averages. Where multiple doses were reported by the same article, a weighted average was taken and combined for all relevant doses.[61,69] Where mean and SD were not available, SD was calculated from the standard error of the mean (SEM), or values were estimated using methodology from the Cochrane Handbook.[73] Where median and interquartile range (IQR) were provided, mean and SD were estimated with the widely used methodology described by Wan et al, 2014.[74] In the minority of cases where the necessary SDs were not available, in the first instance, data were sought from corresponding authors. Failing this, values were imputed using validated methodology described by Ma et al, 2008.[70] Trials were grouped based on comparability and analysed as subgroups. Random effects meta-analyses were undertaken using Review Manager (RevMan) 5.3, Copenhagen: Nordic Cochrane Centre, 2014. Mean difference (MD) was used for outcomes recorded using the same method, and standard mean difference (SMD) for outcomes that were measured using different methodology, each accompanied by 95% confidence intervals [95% CI]. Heterogeneity was assessed using the I^2 statistic and

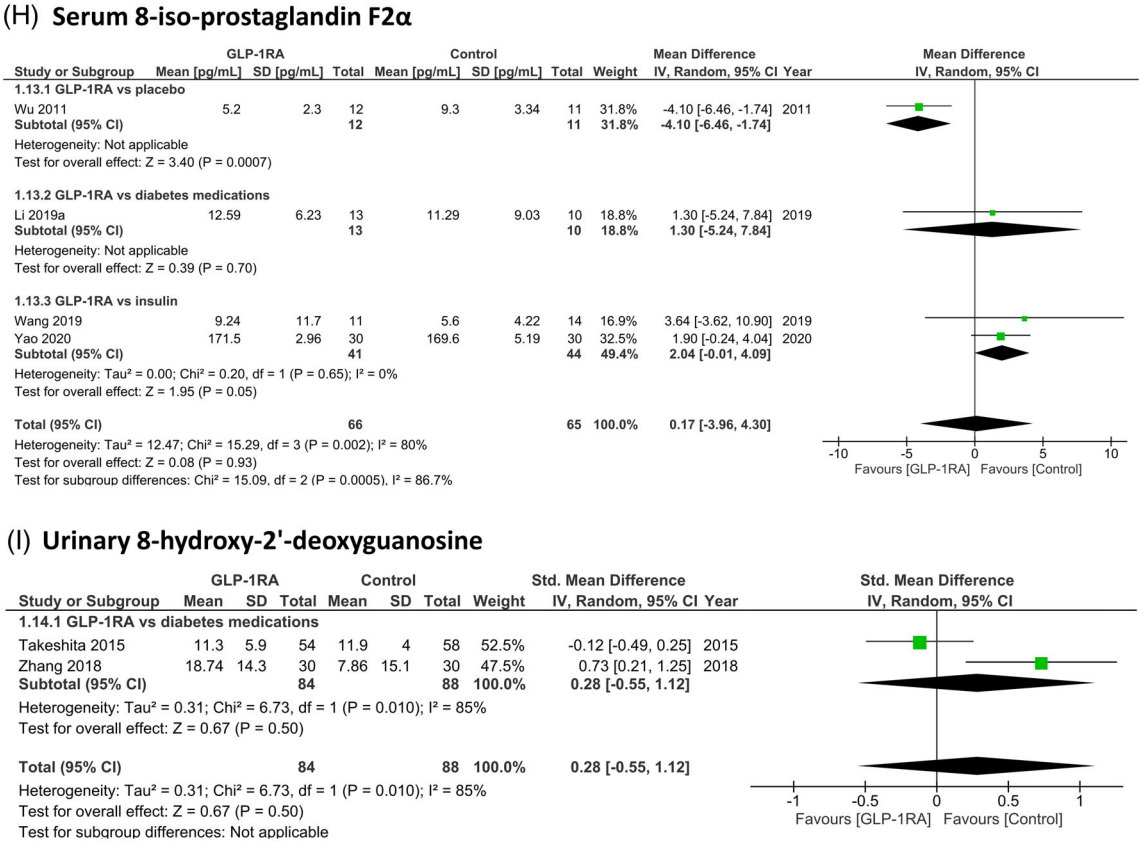

FIGURE 2 (Continued)

funnel plots were visually inspected for publication bias (Figure S1A-I). Statistical tests were calculated using IBM SPSS (version 25). An α value of <0.05 was considered significant. Sensitivity analysis was performed to assess the robustness of the data analysed, eligibility criteria and analysis methods. Dedicated software v. 2019b (Origin Lab, Northampton, Massachusetts) was used to produce graphs. "n" represents the number of participants randomised.

3 | RESULTS

In accordance with the PRISMA checklist,[29] our search of Medline, Embase and the Cochrane Library identified 1702 articles (1061 inflammation, 641 oxidative stress; Figure 1). Of these, 40 RCTs were found to be eligible (37 inflammation, 13 oxidative stress). Included trials were published from 2008 to 2020 and the majority were of a parallel design (37 parallel, three crossover). They comprised 6749 patients (inflammation evaluated in 6560, oxidative stress in 701 patients), included a median (IQR) study population of 60 (33-122) participants, and had a median (IQR) follow-up of 6 months (84-182 days). Trials recruited from 11 individual countries and were multinational in four cases (14 from China,[30–33,37–39,41,44,47,48,56,58,65] seven from the United States,[36,52,53,59,61,63,68] three international studies,[46,64,66] three from Italy,[49,62,67] three from Japan,[45,55,57] two from Denmark,[50,69] two from Greece,[42,54] two Sweden,[34,35] one from France,[51] one from Germany,[60] one from India,[40] and one from Spain[43]). Participants had a mean age of 53.1 years, 56.3% were women, the mean HbA1c was 55.6 (±8.89) mmol/mol, the mean BMI was 28.8 (±3.52) kg/m^2. Participants had T2DM (39 trials) or prediabetes (three trials), and had a mean diabetes duration of 7.46 (±4.22) years (Table 1). In 16 studies (20.8% of total participants), both the active and control arms were also receiving concomitant metformin,[33,35,40,43,45,48,50–54,61–63,65,67] whereas the presence of concomitant medications was not clear in 11 studies (25.2% of total participants).[30,32,36,38,39,44,47,56–58,64] In three studies (5.8% of total participants) >50% of participants received concomitant metformin and other diabetes medications.[45,51,61] There were specific inclusion criteria in 14 trials including overweight or obese participants,[34,35,38,44–46,49,51,53,61,62,64,67,68] with three trials recruiting patients with coronary artery disease or cardiovascular disease,[35,47,53] two trials recruiting patients with NAFLD[30,31] and one study recruiting patients with albuminuria.[50] The vast majority of trials either used liraglutide or exenatide (liraglutide 22 trials, exenatide 14 trials, dulaglutide three trials, taspoglutide one trial). Liraglutide was most often given as 1.8 mg once daily and exenatide as 10 μg twice daily.

3.1 | Risk-of-bias and quality assessment

Approximately one-third (33.8%) of all included trials were deemed to be at high risk of bias using the Cochrane risk-of-bias tool (CRP 10/25, adiponectin 7/17, TNFα 5/11, IL-6 1/6, leptin 0/4, PAI-1 0/4, MDA 2/3, 8-iso-PGF2α 0/4, and 8-OHdG 1/3; Table S2). Adherence to intervention was flagged in 32.5% of included studies due to concerns around blinding, with this reason alone causing 18/26 high risk study results to be categorised as high risk. Concerns around selection of results and randomisation contributed to the high risk of bias in 6.5% and 3.9% of trials, respectively. The quality of evidence was graded as 'moderate' to 'low' (CRP moderate, adiponectin low, TNFα low, IL-6 low, leptin low, PAI-1 low, MDA moderate, 8-iso-PGF2α low, and 8-OHdG low; Table S3). In outcomes for which effect estimates met significance (CRP, adiponectin, TNFα and MDA), grade was reduced by risk of bias (mainly due to absence of blinding) and inconsistency as heterogeneity could not be fully explained by subgroup analysis.

3.2 | Inflammatory biomarkers

As summarised in Table 2A, a pooled analysis of trials comparing GLP-1RAs versus diabetes therapy or placebo (Total) showed significant reductions in CRP and TNFα (MD −0.54 mg/L [−0.75 to −0.34] I^2 = 77%, P < 0.05; SMD −0.39 [−0.62 to −0.15] I^2 = 57%, P = 0.01, respectively) and a significant increase in adiponectin (SMD +0.30 [0.12 to 0.49] I^2 = 76%, P < 0.05 [Figure 2A-C]). Analysis of IL-6, leptin and PAI-1, derived from fewer trials, showed nonsignificant, negative trends (Figure 2D-F). Subgroup analyses reduced heterogeneity to nonsignificant levels in the majority of subgroups (64%) and demonstrated that the GLP-1RAs versus routine diabetes therapy subgroup contributed most to the effect estimate in CRP, adiponectin and TNFα outcomes (MD −0.74 mg/L [−1.06 to −0.43] I^2 = 82%, P < 0.05; SMD +0.42 [0.03 to 0.81] I^2 = 73%, P < 0.05; SMD −0.60 [−0.98 to −0.22] I^2 = 37%, P > 0.05, respectively). Moreover, comparison of two trials of GLP-1RAs versus sitagliptin or glimepiride also found that IL-6 was significantly reduced with GLP-1RA therapy.[32,37]

3.3 | Oxidative stress biomarkers

Pooled analysis of three trials (221 participants) comparing GLP-1RAs versus metformin or insulin (Total) showed a strong and significant reduction in serum MDA (SMD −0.84 [−1.61 to −0.57] I^2 = 87%, P < 0.05 [Table 2B and Figure 2G]). There was no evidence of any change in serum 8-iso-PGF2α or urinary 8-OHdG with use of GLP-1RAs following pooled analyses (Figure 2H,I). Subgroup analyses reduced heterogeneity in every subgroup to nonsignificant levels, suggesting that the trials investigating change in MDA with GLP-1RAs versus insulin were the main contributor to the effect estimate (SMD −1.19 [−1.82 to −0.57] I^2 = 69%, P > 0.05).

3.4 | Associated clinically relevant measurements

As expected, BMI was significantly reduced (n = 21, P < 0.0001) in the included studies. Moreover, SBP was significantly lower in GLP-1RA-

TABLE 2 Summary of meta-analysis and control-subtracted mean change analysis for the 'Total' group of each biomarker

Biomarker	Trials, n	Cumulative participants, n	Effect estimate, MD or SMD	95% CI	I^2, %	P value (Q test)	Trials with consistent control-subtracted mean changes, n	Trials reporting consistent, significant changes, n
(A) Inflammatory biomarkers								
C-reactive protein	23	4962	−0.54 mg/L†	−0.75, −0.34	77	<.05	20 (80%)	15 (60%)
Adiponectin	17	3690	+0.30‡	0.12, 0.49	76	<.05	11 (65%)	6 (35%)
Tumour necrosis factor-α	11	848	−0.39‡	−0.62, −0.15	57	<.05	8 (73%)	5 (45%)
Interleukin-6	6	307	−0.48‡	−1.22, 0.26	91	<.05	3 (50%)	1 (17%)
Leptin	4	376	−0.44‡	−1.02, 0.15	85	<.05	2 (50%)	1 (25%)
Plasminogen activator inhibitor-1	4	2502	−5.16 ng/mL†	−19.3, 8.97	79	<.05	3 (75%)	1 (25%)
(B) Oxidative stress biomarkers								
Serum malondialdehyde	3	221	−0.84‡	−1.61, −0.06	87	<.05	3 (100%)	3 (100%)
Serum 8-iso-prostaglandin F2 alpha	4	131	+0.17 pg/mL†	−3.96, 4.30	80	<.05	2 (40%)	2 (40%)
Urinary 8-hydroxy-2′-deoxyguanosine	2	172	+0.28‡	−0.55, 1.12	85	<.05	3 (100%)	2 (67%)

Note: 'Total' refers to a collective of all three subgroups per biomarker. Trials (n) refers to the number of trials shown in the meta-analysis. Results from all inflammatory markers are from serum measurements. Columns reporting oxidative stress biomarker control-subtracted mean change and trials significance include trials reporting both serum and urinary biomarkers. Trials with consistent control-subtracted mean changes refers to trials reporting results consistent with the directionality of our meta-analysis effect estimate. Of these, the number of trials that report significant changes are reported in the adjacent column. Further information is found in Table S4.

Abbreviations: CI, confidence interval; MD, mean difference†; SMD, standard mean difference‡.

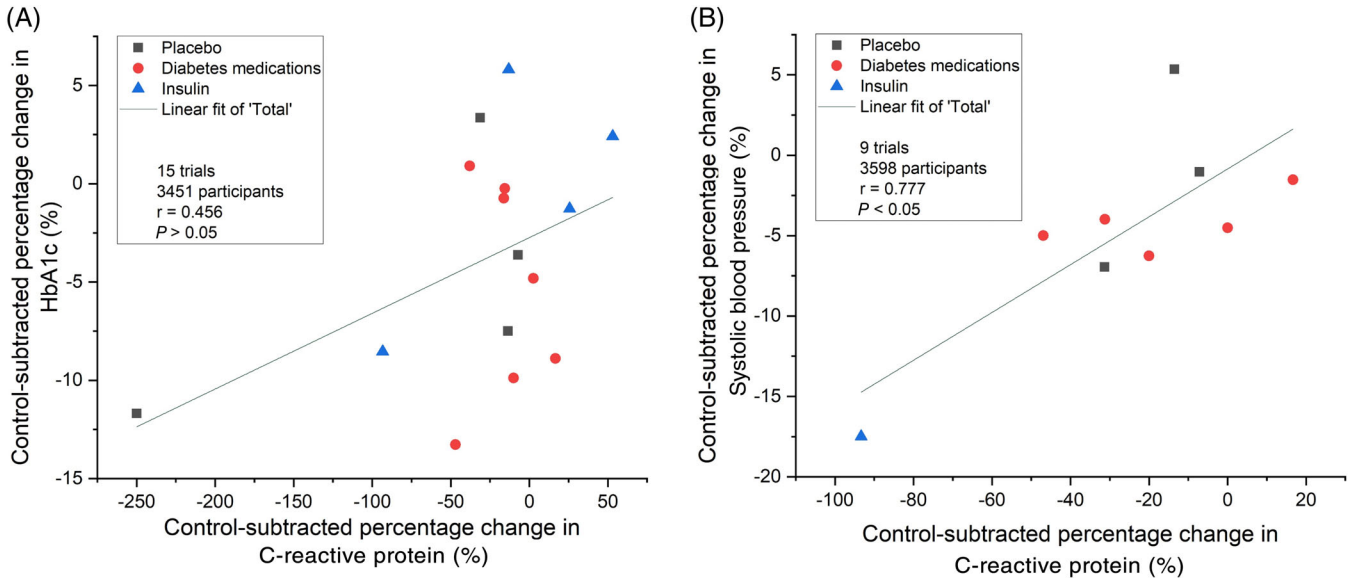

FIGURE 3 Graphs showing the correlation between c-reactive protein and systolic blood pressure (A) and glycated haemoglobin HbA1c (B), with individual subgroups demarked. r, Pearson's correlation coefficient

treated groups (n = 15, $P < 0.05$). Of note, the decrease in SBP was associated with a strong and significant correlation with decrease in CRP (n = 9, r = 0.777, $P < 0.05$ [Figure 3A]). Interestingly, in a small number of trials, change in HOMA-IR was also strongly associated with change in CRP (n = 6, r = 0.898, $P < 0.05$). Change in HbA1c was not associated with changes in any of the inflammatory or oxidative stress biomarkers, including CRP (Figure 3B). Furthermore, change in the following variables were also not associated with change in CRP: follow-up duration; dose of GLP-1RA; BMI; fasting and postprandial glucose; DBP; lipids (LDL, HDL, triglycerides and total cholesterol); liver markers (ALT, AST and GGT); kidney markers (ACR and Cr); and E/A ratio.

3.5 | Sensitivity analyses

The aforementioned results withstood sensitivity analyses examining the specific data analysed, eligibility criteria and analysis methods (Table S5). Following removal of imputed data, changes in CRP, adiponectin and TNFα in the GLP-1RA group compared with the control (Total) remained significant. Mean difference analysis of studies with congruent measurement methodology and scale comparing GLP-1RAs with control (Total) also remained significantly increased for adiponectin and decreased for TNFα. Removal of unblinded studies did not affect the significant reduction in CRP or TNF, or significant increase in adiponectin, but did make MDA nonsignificant. This is probably due to a lack of power caused by removal of studies.

4 | DISCUSSION

This systematic review and meta-analysis of randomised controlled trials examined the effect of GLP-1RAs on biomarkers of low-grade inflammation and oxidative stress to further understand the mechanism behind the cardiorenal protective properties of GLP-1RAs. We found that therapy with GLP-1RAs compared to standard diabetes treatments or placebo was associated with significant reductions in serum CRP, TNFα and MDA and a significant increase in adiponectin. Additionally, SBP was significantly reduced and strongly correlated with the reduction of the inflammatory biomarker CRP. Given the absence of many inflammatory and oxidative stress biomarkers from major cardiovascular and renal outcome trials, this study represents an important synthesis of evidence to inform a deeper understanding of mechanisms influencing the clinical impact of GLP-1RAs and development of similar medications.

The mechanisms by which GLP-1RAs modify cardiovascular and renal outcomes have been grouped into direct and indirect effects. Whilst indirect effects such as improved glycaemic control are likely to be important, glycaemic control alone does not fully explain the reduction in cardiovascular mortality associated with GLP-1RAs.[75] There is increasing evidence that GLP-1RAs act as modulators of atherosclerosis,[76] and their anti-inflammatory and antioxidant properties may contribute to this, as supported by laboratory studies.[77,78] This review demonstrates that these properties remain true within the clinical domain and extend beyond CRP to other biomarkers of inflammation and oxidative stress. However, it was not possible to directly link cardiorenal outcomes to biomarker changes. Although this topic remains controversial, nevertheless there is evidence to suggest that a reduction in elevated CRP[79] and reactive oxygen metabolites[80] is associated with a reduction in major cardiovascular events. We observed that a reduction in CRP was correlated with HOMA-IR. In observational studies, a reduction in HOMA-IR was also associated with a reduction in CRP[81] and cardiovascular risk.[82] GLP-1RAs are known to reduce SBP in people with T2DM,[83] however, the mechanism underlying this effect remains

unclear. Indeed, an association between raised serum CRP and hypertension has been noted in numerous settings, consistent with our data showing reduced SBP with lower CRP levels.[84] We observed that GLP-1RAs are associated with a reduction in TNFα; elevated levels of TNFα have been implicated in endothelial dysfunction in laboratory experiments.[85] Adiponectin has a complex relationship with cardiovascular risk. Meta-analysis of observational studies including people with and without T2DM did not show a benefit of higher adiponectin levels on cardiovascular disease risk.[86] However, in studies of populations with predominantly T2DM, increased adiponectin was associated with a reduction in cardiovascular disease risk.[87,88]

The present study provides a comprehensive overview of the clinical evidence supporting anti-inflammatory effects of GLP-1RAs and to our knowledge is the only systematic review examining their effects on biomarkers of oxidative stress. Previous meta-analyses of observational and randomised studies have demonstrated a reduction in CRP associated with GLP-1RAs,[89,90] but this review is the first to demonstrate that the anti-inflammatory effect of GLP-1RAs extends to TNFα and adiponectin in 40 RCTs with robust sensitivity analyses. Our results are generalisable to clinical medicine because we included comparison with many diabetes treatments, as often patients are on a plethora of therapeutics, whilst simultaneously catering for specific comparison through use of subgroup analysis. We observed that the anti-inflammatory effects of GLP-1RAs on CRP and TNFα remain apparent even when compared with other diabetes medications. Furthermore, subgroup analysis suggested that GLP-1RAs reduce IL-6 when compared with other standard diabetes medications. Another strength of this review is our analysis of associated clinically relevant variables that suggested a link between reduction in SBP and the reduction in CRP with GLP-1RAs. There were fewer trials reporting SBP and other inflammatory biomarkers, which might explain the lack of association between SBP with other inflammatory biomarkers.

In terms of limitations, because larger outcome trials did not examine inflammatory and oxidative stress biomarkers, much of the evidence described is from smaller trials with moderate risk of bias. This is compounded by the short duration of follow-up in some of these trials. Of note, trials that have included biomarkers as secondary outcomes may not necessarily be sufficiently powered to detect changes in biomarkers in isolation. However, considered together, our results are more generalisable and emphasise the importance of an overall synthesis of data, as presented here. One-third of trials were considered to have high risk of bias. This was predominantly due to absence of blinding that as an independent factor led to 69.2% of trials being classed as 'high-risk' (Table S2). It is plausible to predict that blinding of participants and investigators is unlikely to substantially alter the quantitative results of inflammatory and oxidative stress biomarker assays. To manage missing data, we endeavoured to estimate values and, if that was not possible, we imputed values. For example, data reported as medians are likely to be positively skewed due to confounding variables such as illness that may have been missed by the exclusion criteria. However, we argue that conversion of median to mean in this case is more likely to reflect the true effect of GLP-1RAs because the mean value would be influenced less by the skew produced by this confounding variable. Where imputation was necessary, we employed the validated method described by Ma et al.[70] The studies requiring imputation of SDs tended to be larger and thus this method is likely to have overestimated the SD for these trials. This would lead to a more conservative overall effect estimate for our results.

In conclusion, this aggregate level meta-analysis of low- to moderate-quality RCTs is a clinically important synthesis in understanding the anti-inflammatory and antioxidant properties of GLP-1RAs. The present analysis demonstrated a significant reduction in CRP, TNFα, MDA and a significant increase in adiponectin following the use of GLP-1RAs compared with standard diabetes treatments in patients with impaired glucose tolerance. Moreover, reduction in CRP appears to be correlated with a reduction in SBP. Despite the lack of direct evidence from major cardiovascular and renal outcome trials on inflammatory and oxidative stress biomarkers, we believe that this review offers important insights that will inform clinical use of GLP-1RAs and ongoing development of similar medications.

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CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

J.J.H.B. was responsible for conceptualisation, methodology, screening, data collection, investigation, writing the original draft, figure and table construction, formal analysis, quality and risk-of-bias assessment, final review and editing, and project administration. H.F.-D. is responsible for screening, data collection, contribution to the discussion, quality and risk-of-bias assessment, and final review and editing. A.S. contributed to the discussion and final review and editing. A.L.H. assisted with data collection, and final review and editing. D.R.O. reviewed and edited the final manuscript. J.J.H.B. reviewed and edited the final manuscript. J.W.S. conceptualised the review, contributed to investigation and reviewed and edited the final manuscript.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14399.

DATA AVAILABILITY STATEMENT

Data is openly available within the supplementary and cited trials.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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