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Interventions for prediabetes: an umbrella review of systematic reviews and meta-analyses of randomized controlled trials

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A B S T R A C T

Aims: This umbrella review synthesized evidence from systematic reviews and meta-analyses of randomized controlled trials (RCTs) to assess the effectiveness of interventions for preventing adverse outcomes in individuals with prediabetes.

Methods: A total of 23 meta-analyses comprising 602 RCTs and over 30,000 participants were analyzed from databases including Medline, Embase, Web of Science, and Cochrane through February 1, 2025. Interventions evaluated included both pharmacological and non-pharmacological strategies compared to placebo or usual care. Studies reporting only bio-humoral markers were excluded. The GRADE approach was used to assess the certainty of evidence.

Results: Among 15 evaluated interventions, four were supported by high-certainty evidence for diabetes prevention: GLP-1 receptor agonists (RR = 0.26), liraglutide/exenatide/semaglutide (OR = 0.29), orlistat (OR = 0.67), and structured self-care programs (OR = 0.58). High-certainty evidence also supported modest reductions in systolic blood pressure (~2–3 mmHg) from lifestyle interventions, digital health tools, and liraglutide. Significant reductions in BMI and waist circumference were observed with pharmacologic agents, aerobic exercise, and digital platforms. However, metformin combined with lifestyle changes did not yield notable anthropometric benefits.

Conclusion: These findings underscore the value of a multidimensional and personalized approach to prediabetes management, emphasizing evidence-based pharmacological options alongside behavioral and digital health strategies.

Systematic review registration: PROSPERO CRD42025649619.

1. Introduction

Prediabetes represents a crucial stage in the natural history of type 2 diabetes mellitus (T2DM), marked by glucose dysregulation that has not yet met the diagnostic criteria for diabetes but is clearly outside the bounds of normal glycemia [1]. Clinically, this condition includes impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or elevated glycated hemoglobin (HbA1c) levels as defined by major international guidelines, such as the American Diabetes Association (ADA) and the World Health Organization (WHO) [1,2]. Although prediabetes was once considered a relatively benign precursor to diabetes, mounting evidence now supports its role as a significant independent risk factor for cardiovascular disease, chronic kidney disease, neuropathy, retinopathy, and increased all-cause mortality [3]. These findings underscore the clinical urgency of recognizing and treating prediabetes not merely as a warning sign, but as a disease state in its own right.

From a public health perspective, the implications are vast. Globally, the prevalence of prediabetes has reached epidemic proportions, with estimates suggesting that nearly 10 % of adults—more than 480 million people—are currently affected [4]. This number is expected to rise sharply in the coming decades. Importantly, the annual rate of progression from prediabetes to T2DM ranges from 5 % to 10 %, although this can vary based on age, ethnicity, body mass index (BMI), lifestyle factors, and comorbid conditions. This makes prediabetes not only a diagnostic category but also an ideal window for intervention—a window in which reversing or halting the progression of metabolic

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dysfunction is possible.

The recognition of this opportunity has catalyzed a paradigm shift in diabetes prevention. Where treatment of overt diabetes was once the sole focus, contemporary clinical strategies now emphasize early intervention during the prediabetic stage [1]. One of the most important developments in recent years has been the understanding that prediabetes is not a homogeneous entity but a spectrum of metabolic phenotypes. Individuals with isolated IFG, for example, may have different risk profiles and pathophysiological mechanisms compared to those with IGT or elevated HbA1c [5]. This phenotypic heterogeneity has emerged as a hot topic in the field, as researchers investigate whether different subtypes of prediabetes respond differently to therapeutic interventions.

Another pressing area of innovation lies in personalized and digital health interventions. Advances in wearable technology, mobile health (mHealth) applications, and telemedicine platforms are enabling real-time behavioral feedback, remote monitoring, and data-driven coaching [6]. These tools are being integrated into preventive strategies with the goal of increasing adherence, scalability, and long-term sustainability—factors that have historically hindered the success of lifestyle interventions [6]. Tailored behavioral programs and digital therapeutics, often augmented by artificial intelligence, are now considered promising adjuncts to traditional clinical care.

The state of the art in prediabetes intervention includes both lifestyle-based and pharmacological strategies, several of which have demonstrated significant efficacy in delaying or preventing the onset of diabetes. The Diabetes Prevention Program (DPP) in the United States and similar large-scale studies globally have unequivocally shown that structured lifestyle interventions can reduce the incidence of T2DM by up to 58 % over three years [7]. These interventions typically involve dietary modification, increased physical activity (at least 150 min per week of moderate intensity), and behavioral counseling aimed at achieving a modest weight loss of 5–7 % [7].

Pharmacological therapy, particularly with metformin, has also been validated as an effective intervention in high-risk individuals, such as those with BMI $\geq$35 kg/m^2, younger patients, or women with a history of gestational diabetes [8]. In the DPP, metformin reduced diabetes incidence by 31 % compared to placebo [7]. Although not as potent as lifestyle changes, metformin has the advantages of low cost, widespread availability, and a well-established safety profile.

Newer pharmacological agents are also expanding the therapeutic landscape. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as liraglutide and semaglutide, have demonstrated efficacy in not only glycemic control but also significant weight reduction—both key factors in preventing progression to diabetes. A large trial using liraglutide in individuals with obesity and prediabetes showed a reduction in diabetes incidence by over 80 % during treatment [9]. Similarly, sodium-glucose cotransporter-2 (SGLT2) inhibitors are being investigated for their potential to prevent diabetes and improve cardiometabolic outcomes in prediabetic populations [10].

Importantly, despite the wealth of available interventions, there is still no global consensus on how best to integrate and tailor these strategies across diverse healthcare settings for patients affected by prediabetes. This is especially relevant in resource-limited environments where the infrastructure for intensive lifestyle programs or novel medications may be lacking. Moreover, the long-term sustainability of these interventions remains a challenge, as the effectiveness of both pharmacologic and non-pharmacologic therapies tends to wane once active supervision is removed.

Given the multifaceted nature of prediabetes, its far-reaching clinical consequences, and the rapidly evolving therapeutic landscape, the aim of the present umbrella review of systematic reviews and meta-analyses is to provide a comprehensive synthesis of validated interventions for individuals with prediabetes. Moreover, we grade the evidence for each intervention using randomized controlled trials (RCTs) of any pharmacological and non-pharmacological intervention to prevent any negative health outcomes in this condition.

2. Methods

2.1. Protocol and reporting guidance

This umbrella review followed a pre-registered protocol (PROSPERO: CRD42025649619). We followed the guidance of the Preferred Reporting Items for Overviews of Reviews (PRIOR) statement [11].

2.2. Search and study selection process

We searched Embase, Medline, and Web of Science up to February 01st, 2025. A manual search was conducted, including screening the references of all eligible systematic reviews, and searching the Cochrane Database of Systematic Reviews (Ovid CDSR) and the COSMIN Database of Systematic Reviews. The full search key is available in the Supplementary Table 1. Screening at the title/abstract and full text level was conducted by several independent authors (AB, HA, CG, MB), with a third senior member (NV) resolving any conflicts. The references were initially imported in Endnote; Covidence software (https://www.covidence.org/) was used to manage the study selection process.

2.3. Eligibility criteria

Inclusion criteria were i) systematic reviews with meta-analyses, of ii) randomized controlled trials (RCTs), iii) investigating the effect of pharmacological and non-pharmacological interventions versus placebo or standard/usual care, iv) for preventing any health outcome in v) patients affected by prediabetes. Any diagnosis of prediabetes, according to standardized criteria (such as those suggested by the American Diabetes Association [ADA] [1]) were considered. About health outcomes, we excluded bio-humoral outcomes, such as glycosylated haemoglobin (HbA1c) or fasting plasma glucose (FPG). Moreover, excluded were individual studies, narrative reviews, systematic reviews without meta-analyses, and meta-analyses using active groups. Moreover, we excluded conference abstracts. In case of two or more meta-analyses using the same PICO criteria, the largest in terms of RCTs was included.

2.4. Data extraction

The following data were extracted by two independent authors (FL, DP), at single study level, as reported in the original meta-analyses: first author, year of publication, digital object identifier, country, sample size, mean age, sex, diagnostic criteria for prediabetes, sample size, number of RCTs for a prespecified outcome (k). Any inconsistency was resolved by consensus or with a third author (NV).

2.5. Quality assessment of included meta-analyses

Four authors (AB, HA, CG, MB) rated the methodological quality of the included systematic reviews using “A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)” [12], which ranks the quality of a meta-analysis in one of 4 categories, ranging from “critically low” to “high”, according to 16 predefined items. Another author (JD) double checked this evaluation.

2.6. Data analysis and grading of evidence

The data analysis was conducted using STATA 14.0. For each meta-analysis, we estimated the common effect size and its 95 %CI (confidence interval) under the assumption of a random-effects model [13]. Heterogeneity was estimated using the I^2 statistics: values of 50 % or greater are indicative of high heterogeneity, while values above 75 % suggest very high heterogeneity [14]. Publication bias was assessed using the test proposed by Egger and co-workers [15].

The evidence from meta-analyses was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and

Evaluation) assessment [16]. The GRADE framework takes into account several important domains for the judgment of the certainty of the evidence, including study design, risk of bias, inconsistency, indirectness, imprecision and other aspects, such as publication bias and the outcomes of interest [16]. The certainty of the evidence was then evaluated in very low (the true effect is probably markedly different from the estimated effect), low (the true effect might be markedly different from the estimated effect), moderate (the true effect is probably close to the estimated effect) or high (there is a lot of confidence that the true effect is similar to the estimated effect) [16]. The data are reported by the setting originally declared in the systematic review.

3. Results

3.1. Literature search

As reported in Supplementary Table 1, we initially identified 1570 records across three major databases. Using Endnote, 516 duplicates were initially removed obtaining, as shown in Fig. 1, 1054 articles to screen. Covidence found other 252 duplicates, therefore giving 802 articles to screen. Of them, 154 full-texts were evaluated: after excluding 131 articles, mainly based on the fact that they included outcomes not eligible for our umbrella review, we obtained 23 eligible full texts, published between 2011 and 2024 [17–39]. The list of excluded references, with reason, is reported in Supplementary Table 2.

3.2. Descriptive findings

Overall, the 23 systematic reviews and meta-analyses reported data about 77 different comparisons divided in this umbrella review in three major categories, i.e., risk of diabetes (Table 1), cardiovascular diseases outcomes (Table 2) and anthropometric measures and quality of life parameters (Table 3). In total, the 23 systematic reviews and meta-analyses included approximately 602 single RCTs for a total of 30,193 patients affected by prediabetes.

3.3. Effects of interventions to decrease the risk of diabetes in prediabetes

Table 1 summarises the findings of the comparisons using, as outcome, diabetes incidence. Overall, we found 15 comparisons: of them, four were ranked as high according to the GRADE evaluation for the level of evidence. In four RCTs, orlistat, compared to placebo, significantly decreased the risk of diabetes of 37 % (OR = 0.67; 95 %CI: 0.49–0.82; p = 0.01). Similarly, both GLP-1Ras, with a daily dosage between 2 and 3 mg, in 14 RCTs, including 12110 patients with prediabetes, decreased the risk of prediabetes of 74 % (RR = 0.26; 95 %CI: 0.19–0.35, p < 0.0001). A similar effect was observed for liraglutide, exanatide and semaglutide (n = 6 RCTs, sample size = 3886, OR = 0.29;

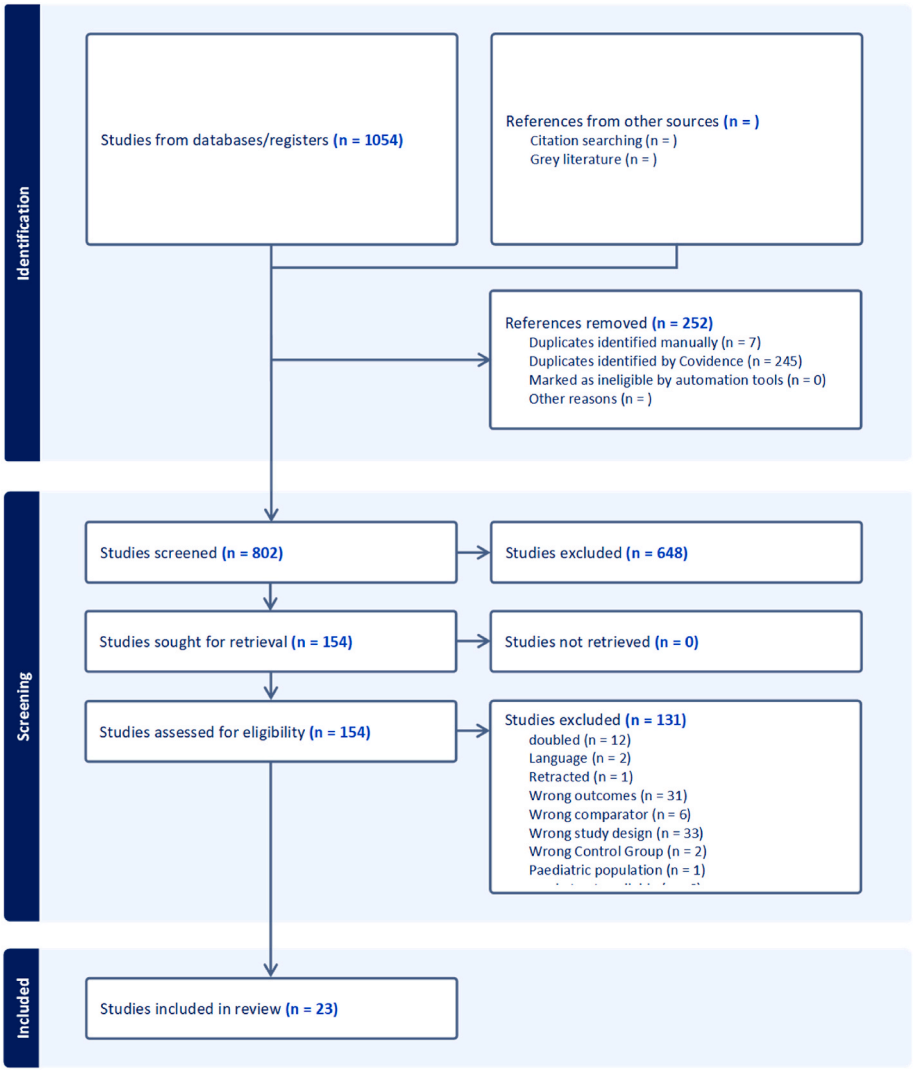

Fig. 1. PRISMA flowchart.

Table 1
Interventions in participants with prediabetes to decrease the risk of having diabetes.

Intervention	Dosage of intervention	Outcome	Number of RCTs	Sample size	Type of metric	Mean ES (RE)	LL	UL	P-value	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE
Orlistat [21]	Not reported	Diabetes	4	976	RR	0.63	0.49	0.82	0.01	Not serious	Not serious	no	Not serious	yes	**HIGH**
GLP-1RAs [31]	2–3 mg daily	Diabetes	14	12110	RR	0.26	0.19	0.35	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Self-care programs [34]	Not reported	Diabetes	13	7323	OR	0.58	0.46	0.73	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Liraglutide, exenatide, semaglutide [36]	1.8–3 mg daily	Diabetes	6	3886	OR	0.29	0.16	0.5	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Lifestyle [29]	Various	Diabetes	37	12804	RR	0.59	0.52	0.67	<0.0001	Not serious	Serious	no	Not serious	no	**MODERATE**
SGLT2 [26,33]	10 mg	Diabetes	7	11310	HR	0.8	0.71	0.89	<0.0001	Not serious	Not serious	no	Serious	no	**MODERATE**
Vitamin D 3 [38]	20,000–88,865 IU/ week	Diabetes	11	9086	RR	0.89	0.82	0.96	0.004	Not serious	Not serious	no	Serious	no	**MODERATE**
Metformin + lyfstyle intervention [18]	500–1700 mg/day + physical activity	Diabetes	5	2294	RR	0.85	0.75	0.96	0.008	Serious	Not serious	no	Serious	no	**LOW**
Acarbose [24]	25–100 mg TID	Diabetes	8	2120	RR	0.42	0.26	0.66	<0.0001	Not serious	Serious	no	Not serious	yes	**LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Diabetes	13	5203	OR	0.73	0.58	0.93	0.01	Very serious	Not serious	no	Not serious	no	**VERY LOW**
Drug and non drug approach [22]	Various	Diabetes	12	30442	RR	0.66	0.55	0.8	<0.0001	Very serious	Very serious	no	Not serious	no	**VERY LOW**
Traditional Chinese medicine + lifestyle [27]	Various	Diabetes	17	3424	RR	0.52	0.45	0.61	<0.0001	Very serious	Not serious	no	Not serious	no	**VERY LOW**
Lifestyle intervention [25]	Not reported	Diabetes	15	8563	RR	0.78	0.72	0.85	<0.0001	Very serious	Not serious	no	Serious	yes	**VERY LOW**
Metformin [37]	500–1700 mg/daily	Diabetes	17	1601	RR	0.42	0.29	0.61	<0.0001	Very serious	Not serious	no	Not serious	no	**VERY LOW**

Abbreviations: ES, effect size; HR, hazards ratio; LL, lower limit; OR, odds ratio; RCT, randomized controlled trial; RE, random effect; RR, relative risk; UL, upper limit.

Table 2
Interventions in participants with prediabetes to decrease the risk of having cardiovascular outcomes and mortality.

Intervention	Dosage of intervention	Outcome	Number of RCTs	Sample size	Type of metric	Mean ES (RE)	LL	UL	P-value	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE
Metformin + lifestyle intervention [18]	500–1700 mg/day + physical activity	Diastolic blood pressure	4	1882	SMD	0.04	−0.05	0.13	0.38	Not serious	Not serious	no	Not serious	no	**HIGH**
Yoga [30]	Not reported	Diastolic Blood Pressure	15	1420	SMD	0.01	−0.1	0.12	0.86	Not serious	Not serious	no	Not serious	no	**HIGH**
Lifestyle intervention [32]	Not reported	Diastolic Blood Pressure	5	1673	MD	−2.16	−3.07	−1.24	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Pharmacological interventions [32]	Not reported	Diastolic Blood Pressure	3	2373	MD	−0.36	−1.16	0.43	0.37	Not serious	Not serious	no	Not serious	no	**HIGH**
Liraglutide [36]	1.8–3 mg daily	Diastolic Blood Pressure	4	2454	MD	−0.52	−1.26	0.21	0.16	Not serious	Not serious	no	Not serious	no	**HIGH**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Diastolic blood pressure mean difference	4	2546	MD	−1.1	−2	−0.2	0.02	Not serious	Not serious	no	Not serious	no	**HIGH**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Diastolic blood pressure change score	6	1246	MD	−1.17	−2.4	0.07	0.07	Not serious	Not serious	no	Not serious	no	**HIGH**
Metformin + lifestyle intervention [18]	500–1700 mg/day + physical activity	Systolic blood pressure	5	1940	SMD	−0.05	−0.14	0.04	0.29	Not serious	Not serious	no	Not serious	no	**HIGH**
Any pharmacological intervention [32]	Various	Systolic Blood Pressure	3	2373	MD	−2.74	−3.91	−1.58	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Liraglutide [36]	1.8–3 mg daily	Systolic Blood Pressure	4	2454	MD	−2.76	−3.78	−1.74	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Systolic blood pressure change score	7	1403	MD	−2.11	−3.86	−0.36	0.02	Not serious	Not serious	no	Not serious	no	**HIGH**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Systolic blood pressure mean difference	4	2546	MD	−0.93	−3.1	1.24	0.4	Not serious	Not serious	no	Not serious	no	**HIGH**
Lifestyle [25]	150 min/weekly physical activity	All-cause mortality	7	4210	RR	0.84	0.37	1.9	0.68	Not serious	Not serious	no	Serious	no	**MODERATE**
Medical Nutrition Therapy [19]	60–90 min/session	Diastolic Blood Pressure	9	1569	MD	−2.59	−3.84	−1.34	<0.0001	Serious	Not serious	no	Not serious	no	**MODERATE**
Medical Nutrition Therapy [19]	60–90 min/session	Systolic Blood Pressure	9	1569	MD	−4.33	−6.69	−1.79	0.001	Serious	Not serious	no	Not serious	no	**MODERATE**
Yoga [30]	Not reported	Systolic Blood Pressure	15	1245	SMD	−0.06	−0.17	0.05	0.31	Not serious	Not serious	no	Not serious	yes	**MODERATE**
Lifestyle [32]	Not reported	Systolic Blood Pressure	5	1673	MD	−3.51	−6.36	−0.66	0.02	Not serious	Serious	no	Not serious	no	**MODERATE**
Lifestyle [32]	Not reported	Cardiovascular events	2	738	RR	0.87	0.22	3.48	0.84	Not serious	Serious	no	Serious	NA	**LOW**
Drug and non-drug approach [22]	Not reported	All-cause mortality	10	17317	RR	0.95	0.83	1.08	0.4	Very serious	Not serious	no	Serious	no	**VERY LOW**
Lifestyle intervention [39]	Not reported	All-cause mortality	7	6013	RR	0.91	0.71	1.16	0.45	Very serious	Not serious	no	Serious	no	**VERY LOW**
Drug and non-drug approach [22]	Not reported	cardiovascular death	7	20952	RR	1.04	0.62	1.75	0.88	Very serious	Serious	no	Serious	no	**VERY LOW**

(*continued on next page*)

Table 2 (*continued*)

Intervention	Dosage of intervention	Outcome	Number of RCTs	Sample size	Type of metric	Mean ES (RE)	LL	UL	P-value	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE
Lifestyle intervention [39]	Not reported	Cardiovascular death	3	2815	RR	0.97	0.55	1.69	0.91	Serious	Serious	no	Serious	no	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Diastolic blood pressure follow-up	10	2016	MD	−2.7	−5.02	−0.39	0.02	Very serious	Very serious	no	Not serious	no	**VERY LOW**
Drug and non-drug approach [22]	Not reported	Myocardial infarction	4	14957	RR	0.63	0.27	1.51	0.3	Very serious	Serious	no	Not serious	no	**VERY LOW**
Drug and non-drug approach [22]	Not reported	Stroke	3	14957	RR	0.76	0.58	0.98	0.04	Very serious	Not serious	no	Not serious	no	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Systolic blood pressure follow-up	10	2016	MD	−1.32	−4	1.36	0.34	Very serious	Very serious	no	Not serious	no	**VERY LOW**

Abbreviations: ES, effect size; LL, lower limit; MD, mean difference; RCT, randomized controlled trial; RE, random effect; RR, relative risk; SMD, standardized mean difference; UL, upper limit.

95 %CI: 0.16–0.50) and for self-care programs (n = 13 RCTs, sample size = 7323, OR = 0.58; 95 %CI: 0.46–0.73). Three comparisons were ranked as moderate, including lifestyle interventions (physical activity level of 150–180 min weekly of moderate activity), SGLT2 and vitamin D3 supplementation (20,000–88,865 IU weekly) (Table 1). The use of acarbose and the combination of metformin and lifestyle interventions only slightly decreased the risk of diabetes (low level of evidence according to the GRADE), whilst the other six comparisons as very low.

3.4. Effects of interventions to decrease the risk of cardiovascular outcomes and mortality

Table 2 shows the findings about cardiovascular outcomes and outcomes, in patients with prediabetes. Overall, we found 25 independent comparisons mainly about blood pressure (n = 18), followed by all-cause mortality (n = 3) and cardiovascular death (n = 2), myocardial infarction (n = 1) and stroke (n = 1).

Only the outcomes about blood pressure were ranked as high according to the GRADE (n = 12). Overall, only five comparisons showed that the interventions were better than the control groups (placebo or no intervention) in improving blood pressure parameters, namely: lifestyle interventions (n = 5 RCTs, sample size = 1673, MD = −2.16 mmHg, 95 %CI: 3.07 to −1.24, $p < 0.0001$) and digital health interventions (n = 4 RCTs, sample size = 2546, MD = −1.1 mmHg, 95 %CI: 2 to −0.2, p = 0.02) to decrease diastolic blood pressure and any pharmacological interventions, liraglutide and digital health interventions to decrease systolic blood pressure with a mean decrease around 2.5 mmHg (Table 2). On the contrary, we are highly confident that the combination of metformin and lifestyle interventions, yoga, any pharmacological intervention, liraglutide and digital health interventions did not substantially modify diastolic blood pressure compared to no intervention or placebo in prediabetes similarly to metformin and lifestyle interventions for systolic blood pressure.

About all-cause mortality, we found that lifestyle interventions and the combination of drug and non-drug approaches did not decrease the risk of this outcome in prediabetic subjects, similarly to cardiovascular death: all these outcomes were supported by a level of evidence between moderate to very low. The combination of drug and non-drug interventions significantly decreased the risk stroke in 3 RCTs, n = 14957, RR = 0.76, 95 %CI: 0.58–0.98, p = 0.04 (very low certainty of evidence according to the GRADE), while drug and non-drug interventions did not affect the risk of myocardial infarction in prediabetes (Table 2).

3.5. Effects of interventions for anthropometric measures and quality of life

Table 3 indicates the data about anthropometric measures and quality of life. Overall, 35 comparisons were found. According to the GRADE evaluation, only six comparisons were ranked as high as level of evidence, five moderate, one low, and 23 as very low. Among comparisons evaluated as high, the use of any pharmacological interventions and aerobic exercise significantly decreased the values of body mass index (BMI) compared to the controls (pharmacological interventions: n = 3 RCTs, 2373 patients, MD = −1.7 kg/m^2; 95 %CI: 1.93 to −1.47, $p < 0.0001$; aerobic exercise: n = 11 RCTs, 2403 patients, MD = −1.58 kg/m^2; 95 %CI: 1.94 to −1.22, $p < 0.0001$); similarly, digital health lifestyle interventions were able to decrease waist change score of 2.07 cm (95 % CI: 2.87 to −1.26) in 5 RCTs and 954 patients affected by prediabetes and of 1.75 cm (95 %CI: 2.45 to −1.06) in 4 RCTs and 2546 participants. Furthermore, liraglutide with a dose between 1.8 and 3 mg daily significantly decreased waist circumference of 3.67 cm (95 %CI: 4.27 to −3.06) in four RCTs including 2454 people with prediabetes. On the contrary, in 7 RCTs (n = 2100 patients affected by prediabetes), the combination of metformin and lifestyle interventions did not significantly decrease BMI values compared to controls (p = 0.62), supported by a high level of certainty of evidence (Table 3).

Table 3
Interventions in participants with prediabetes for anthropometric measures and quality of life.

Intervention	Dosage of intervention	Outcome	Number of RCTs	Sample size	Type of metric	Mean ES (RE)	LL	UL	P	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE
Metformin + lifestyle intervention [18]	500–1700 mg/day + physical activity	BMI	7	2100	SMD	−0.02	−0.11	0.06	0.62	Not serious	Not serious	no	Not serious	no	**HIGH**
Pharmacological interventions [32]	Not reported	BMI	3	2373	MD	−1.7	−1.93	−1.47	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Aerobic exercise [35]	3–24 months	BMI	11	2403	WMD	−1.58	−1.94	−1.22	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Waist change score	5	954	MD	−2.07	−2.87	−1.26	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Liraglutide [17]	1.8–3 mg daily	Waist circumference	4	2454	MD	−3.67	−4.27	−3.06	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Waist mean difference	4	2546	MD	−1.75	−2.45	−1.06	<0.0001	Not serious	Not serious	no	Not serious	no	**HIGH**
Metformin + lifestyle intervention [18]	500–1700 mg/day + physical activity	Body weight	4	2863	SMD	0.13	−0.02	0.28	0.09	Not serious	Serious	no	Not serious	no	**MODERATE**
Metformin + lifestyle intervention [18]	500–1700 mg/day + physical activity	Waist circumference	3	1771	SMD	0.006	−0.09	0.1	0.90	Serious	Not serious	no	Not serious	no	**MODERATE**
Medical Nutrition Therapy [19]	60–90 min/ session	Waist circumference	9	1559	MD	−2.94	−3.52	−2.37	<0.0001	Serious	Not serious	no	Not serious	no	**MODERATE**
Medical Nutrition Therapy [19]	60–90 min/ session	Weight	9	1559	MD	−3.24	−4	−2.49	<0.0001	Serious	Not serious	no	Not serious	no	**MODERATE**
Liraglutide [36]	1.8–3 mg daily	Weight	5	2605	MD	−4.13	−4.88	−3.38	<0.0001	Not serious	Serious	no	Not serious	no	**MODERATE**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	BMI mean difference	3	1110	MD	−0.58	−1.27	0.11	0.1	Serious	Serious	no	Not serious	no	**LOW**
Medical Nutrition Therapy [19]	60–90 min/ session	BMI	10	1673	MD	−1.63	−2.37	−0.9	<0.0001	Serious	Very serious	no	Not serious	no	**VERY LOW**
Prebiotic supplementation [23]	2–15 g/day	BMI	5	316	SMD	−0.04	−0.26	0.18	0.71	Serious	Not serious	no	Very serious	no	**VERY LOW**
Traditional Chinese Patent medicine + lifestyle [27]	0.24–11.6 g daily	BMI	13	2449	MD	−0.42	−0.74	−0.1	0.01	Very serious	Very serious	no	Not serious	no	**VERY LOW**
Lifestyle intervention [32]	Not reported	BMI	6	1529	MD	−0.95	−1.48	−0.41	0.001	Serious	Very serious	no	Not serious	no	**VERY LOW**
Liraglutide [17]	1.2–3 mg/day	BMI	4	2412	MD	−1.61	−2.73	−0.496	0.005	Not serious	Very serious	no	Not serious	no	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	BMI change score	24	3828	MD	−0.54	−0.78	−0.31	<0.0001	Very serious	Serious	no	Not serious	no	**VERY LOW**

(*continued on next page*)

Table 3 (*continued*)

Intervention	Dosage of intervention	Outcome	Number of RCTs	Sample size	Type of metric	Mean ES (RE)	LL	UL	P	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	GRADE
Prebiotic supplementation [23]	1.5–30 g/day	Body Fat percentage	7	306	SMD	−1.27	−2.33	−0.22	0.02	Serious	Very serious	no	Very serious	no	**VERY LOW**
Lifestyle intervention [32]	Not reported	Hip circumference	2	162	MD	−2.88	−5.08	−0.68	0.01	Very serious	Serious	no	Very serious	NA	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Quality of life (mental health component)	3	118	MD	2.45	−0.04	4.94	0.05	Not serious	Not serious	no	Very serious	no	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Quality of life (physical health component)	3	118	MD	2.28	0.65	3.91	0.006	Not serious	Not serious	no	Very serious	no	**VERY LOW**
Prebiotic supplementation [23]	1.5–6 g/day	Waist circumferemce	4	334	SMD	−0.34	−0.77	0.09	0.13	Very serious	Serious	no	Very serious	no	**VERY LOW**
Liraglutide [36]	1.8–3 mg/day	Waist circumference	4	2424	MD	−4.35	−4.9	−3.98	<0.0001	Not serious	Very serious	no	Not serious	no	**VERY LOW**
Yoga [30]	Not reported	Waist circumference	16	1751	SMD	0.02	−0.21	0.25	0.86	Not serious	Very serious	no	Not serious	no	**VERY LOW**
GLP-1RAs [31]	1.8–3 mg	Waist Circumference	4		SMD	−3.48	−4.55	−2.42	<0.0001	Serious	Not serious	no	Very serious	no	**VERY LOW**
Lifestyle intervention [32]	Not reported	Waist circumference	7	2051	MD	−2.57	−3.98	−1.16	<0.0001	Not serious	Very serious	no	Not serious	no	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Waist follow-up	12	1970	MD	−1.17	−2.33	−0.01	0.048	Very serious	Not serious	no	Not serious	no	**VERY LOW**
Yoga [27]	Not reported	Weight	10	943	SMD	0.05	−0.34	0.43	0.82	Not serious	Very serious	no	Not serious	no	**VERY LOW**
GLP-1RAs [31]	1.8–3 mg	Weight	8		MD	−6.38	−10.09	−2.67	<0.0001	Not serious	Very serious	no	Very serious	no	**VERY LOW**
Lifestyle intervention [32]	Not reported	Weight	7	2051	MD	−2.28	−3.07	−1.49	<0.0001	Not serious	Very serious	no	Not serious	no	**VERY LOW**
Liraglutide [17]	1.8–3 mg/day	Weight change	4	2424	MD	−3.55	−4.9	−2.21	<0.0001	Not serious	Very serious	no	Not serious	yes	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Weight change follow up	11	2797	MD	−1.57	−3.18	0.03	0.06	Very serious	Not serious	no	Not serious	no	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Weight change mean difference	4	2546	MD	−1.49	−2.72	−0.26	0.02	Not serious	Very serious	no	Not serious	yes	**VERY LOW**
Digital Health Lifestyle Interventions [20]	Daily-annually contact intervention	Weight change score	10	1998	MD	−1.93	−2.62	−1.23	<0.0001	Not serious	Very serious	no	Not serious	no	**VERY LOW**

Abbreviations: ES, effect size; LL, lower limit; MD, mean difference; RCT, randomized controlled trial; RE, random effect; SMD, standardized mean difference; UL, upper limit; WMD, weighted mean difference.

Among the five comparisons supported by moderate level of evidence according to the GRADE, medical nutrition therapy, with session of 60–90 min, was able to significantly improve both waist circumference and weight in people with prediabetes as well as liraglutide using weight loss as outcome, whilst the combination of metformin and lifestyle interventions did not modify body weight or waist circumference as outcomes.

3.6. Quality assessment

Supplementary Table 3 reports the evaluation about the quality of the meta-analyses included. Among the 23 meta-analyses included, five were evaluated as high at AMSTAR 2, four as moderate, ten as low and the other four as critically low.

4. Discussion

This umbrella review systematically evaluated the effectiveness of pharmacological and non-pharmacological interventions in preventing adverse health outcomes among individuals with prediabetes. Including 23 meta-analyses comprising over 600 randomized controlled trials and involving more than 30,000 participants, the findings could be of clinical importance about the possible treatments for prediabetes.

4.1. Clinical relevance

The prevention of the transition from prediabetes to diabetes, is probably, the most important and explored outcome in people affected by prediabetes. Four interventions achieved a high level of evidence according to the GRADE evaluation, indicating that these interventions must be recommend in prediabetes. First, GLP-1RAs demonstrated the most profound impact, reducing diabetes incidence by 74 %. The mechanism likely relates to GLP-1RAs' ability to enhance insulin secretion, inhibit glucagon, delay gastric emptying, and promote satiety, leading to substantial weight loss—a key factor in improving insulin sensitivity [40]. Additionally, anti-inflammatory properties may further enhance metabolic outcomes [40]. Similarly, liraglutide, exenatide, and semaglutide, as single agents, achieved similar results with a 71 % reduction in diabetes risk. Furthermore, our umbrella review shows that orlistat is also of importance to prevent the transition from prediabetes to diabetes. Orlistat acts by inhibiting intestinal lipases, reducing fat absorption. The primary benefit is weight loss, which, though modest, can substantially improve insulin resistance and glycemic control, finally preventing the onset of diabetes [41]. Unfortunately, checking the ADA guidelines for prediabetes [1], despite all these interventions are supported by a high certainty of level, meaning that these interventions are highly effective in prediabetes, but still not recognized of clinical importance. On the other hand, we also found that self-Care Programs, including structured lifestyle coaching, could reduce the diabetes incidence by 42 %. These programs often integrate dietary advice, physical activity promotion, and behavioral support, contributing to both metabolic and psychological improvements. We believe that these interventions provide clinicians with a diverse toolkit for diabetes prevention. Pharmacological approaches may be particularly suitable for patients with clinical obesity or a high cardiovascular risk profile, while behavioral interventions are cost-effective and scalable, making them attractive for population-level implementation.

Although it is known that prediabetes is a known risk factor for CVD outcomes, few interventions in this review were shown to reduce major CVD events or mortality. However, blood pressure outcomes—a key intermediate cardiovascular risk factor—were more responsive. Briefly, lifestyle interventions achieved significant reductions in both systolic (mean difference ~ −3.5 mmHg) and diastolic BP (~−2.2 mmHg), whilst digital health interventions also demonstrated consistent reductions (systolic: ~ −2.1 mmHg, diastolic: ~ −1.1 mmHg), supported by a high level of evidence. Liraglutide and other pharmacologic agents showed small but statistically significant reductions in systolic BP (~−2.7 mmHg). A clinically meaningful reduction in blood pressure to obtain a positive clinical effect typically involves a decrease of 5–10 mmHg in systolic blood pressure or 3–5 mmHg in diastolic blood pressure [42]. These decreases, as widely known, are reported to be of importance to further decrease the CVD risk [42]. Unfortunately, in our umbrella review, no one of the proposed interventions reached these clinically important cut-offs. Similarly, we were unable to find any significant effect on all-cause mortality, myocardial infarction or cardiovascular death independently from the intervention. This unexpected finding is probably due to the fact that the studies included in the meta-analyses considered were probably unpowered to detect any significant difference between the intervention and the control groups proposed. Therefore, while CVD event and mortality reduction remains unproven in prediabetes, clinicians should still prioritize blood pressure control as a modifiable risk factor.

Finally, this umbrella review highlighted several interventions that achieved significant improvements in anthropometric outcomes. Among the interventions ranked high by the GRADE, we cite some pharmacological Interventions, such as liraglutide, able to reduce in mean 3.67 cm in waist circumference. Of importance, aerobic exercise resulted in a BMI reduction of −1.58 kg/m^2, compared to controls as well as digital Health Lifestyle Programs, able to reduce, in mean, the waist circumference by ~2 cm. Interestingly, the combination of metformin and lifestyle interventions, despite being widely recommended worldwide [43], did not lead to significant reductions in BMI, body weight, or waist circumference compared to controls—even though the GRADE ranking was high, overall indicating that the use of metformin is not recommended in prediabetes. Based on our findings, this could suggest that lifestyle interventions, when not tailored or intensively supervised, may lose efficacy over time, being unable to decrease the risk of obesity.

4.2. Limitations

Despite the comprehensive scope and robust methodology, this umbrella review has several limitations. First, although systematic reviews were included, the heterogeneity in intervention protocols, diagnostic criteria, and follow-up duration complicates cross-comparison. Second, it is possible that some outcomes, especially in cardiovascular domains, were inconsistently defined or underpowered to detect differences between treated and control groups. Finally, according to AMSTAR 2, only 5 of 23 included meta-analyses were ranked as high quality, which may limit the confidence in certain results.

5. Conclusions

In conclusion, this umbrella review underscores that several interventions can substantially reduce the risk of diabetes progression in individuals with prediabetes, particularly GLP-1 receptor agonists, orlistat, and structured self-care programs. Additionally, significant improvements in blood pressure and anthropometric parameters highlight the broader metabolic and cardiovascular benefits of early intervention. Clinicians should consider both pharmacologic and non-pharmacologic strategies in a personalized manner based on patient risk profiles, preferences, and resource availability. Future research should focus on the durability of intervention effects, cost-effectiveness analyses, and exploration of synergistic combinations, particularly in real-world settings. Bridging the gap between evidence and implementation remains essential for curbing the global burden of diabetes and its complications.

Novelty statement

This umbrella review provides the most up-to-date and highest-level synthesis of evidence on pharmacological and non-pharmacological interventions for prediabetes using GRADE methodology. Unlike

traditional systematic reviews that focus on one intervention class, this review integrates evidence across pharmacotherapy, lifestyle, and digital health domains. It offers a novel, comparative overview that clinicians and policymakers can use to personalize prediabetes management.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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