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Intensive management of obesity in people with severe chronic kidney disease: a review

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Abstract

Obesity is highly prevalent worldwide, including among people with chronic kidney disease. The presence of severe and/or end-stage kidney disease, complicates the treatment of obesity for several reasons, including restrictions on protein and fluid intake and renal excretion of several medications indicated for the treatment of obesity. The aim of this review is to assess the safety of intensive obesity treatments, such as very-low-energy diets (VLEDs), obesity pharmacotherapy and/or bariatric surgery, in people with end-stage kidney disease. A literature search was conducted to identify studies reporting safety outcomes for very-low-energy diets, liraglutide, phentermine, phentermine-topiramate, naltrexone-bupropion and bariatric surgery in people with eGFR <30 mL/min/1.73m^2 or on dialysis. Limited data was insufficient to recommend VLEDs but highlighted their potential efficacy and the need for close clinical and biochemical monitoring. There was no data regarding centrally-acting obesity pharmacotherapy in this population, although some GLP-1 analogues appear to safely induce weight loss at doses used for the treatment of type 2 diabetes. Some studies suggest an increased rate of complications of bariatric surgery in individuals with severe or end-stage CKD. Further prospective evaluation of intensive obesity management in the growing population with obesity and severe, end-stage and dialysis-dependent CKD is required.

Introduction

The prevalence of both chronic kidney disease (CKD) and obesity have increased by 30-50% over the last three decades.[1, 2] In 2016-17, more than 697 million cases of CKD were recorded,[1] and more than 650 million people had obesity.[3]

Obesity is a well-established independent risk factor for the development and progression of CKD. Large cohort studies show associations between higher body mass index (BMI) and lower glomerular filtration rate (GFR), albuminuria and end-stage kidney disease (ESKD), even after adjusting for other CKD risk factors such as hypertension and diabetes mellitus.[4, 5] Pathophysiological changes associated with obesity include adipose tissue inflammation, insulin resistance, increased tubular sodium reabsorption and hyperfiltration, which lead to progressive kidney injury (reviewed in detail in Docherty and le Roux).[6]

In people with obesity and CKD, weight loss can improve renal outcomes and slow CKD progression. A systematic review and meta-analysis of weight loss interventions in people with non-dialysis dependent CKD found a mean reduction in BMI of 16.5 kg/m^2 in observational studies of bariatric surgery, with reduction (normalisation) of eGFR in patients with hyperfiltration, and reduction in albuminuria.[7] Hypocaloric diet interventions achieved a much smaller mean BMI reduction of 3.7 kg/m^2, and were associated with an improvement in proteinuria, but not GFR, over a mean follow up of 7 months.[7]

Lifestyle intervention, comprising diet, physical activity and behaviour modification, is the cornerstone of obesity management, and typically results in mean weight loss of 5-8 kg over 6-12 months followed by gradual weight regain.[8] Weight loss of this magnitude has demonstrated cardiometabolic benefits, but may fall short of treatment goals, meaning that consideration needs to be given to more intensive interventions, such as very-low-energy diets (VLEDs), obesity pharmacotherapy and bariatric surgery.[8] However, the complexity and potential risks associated with these more demanding interventions may be greater in the presence of ESKD for various reasons, such as the potential for severe caloric

restriction to exacerbate the sarcopenia associated with ESKD, restrictions on protein and fluid intake,[9] and renal excretion of a number of medications indicated for obesity treatment.[10, 11] While hypocaloric diet and exercise interventions have demonstrated safety in people with moderate (predominantly stage 3-4) CKD,[12, 13] the safety of more intensive obesity treatments in the setting of severe and end-stage CKD has not been established (stages of CKD are given in **Table 1**). This is an issue of growing importance in the context of the rising prevalence of obesity, and the common inclusion of BMI cut-offs of 30-35 kg/m^2 in eligibility criteria for kidney transplantation listing.[14] Therefore, the aim of this literature review is to assess the safety of approved treatments for obesity beyond lifestyle intervention - VLEDs, pharmacotherapy, and bariatric surgery - in people with severe or end-stage CKD.

Materials and Methods

Search strategy and eligibility

One reviewer searched Ovid Medline (1949 to 2020) and EMBASE (1974 to 2020) between 16 and 18 June 2020. Articles were included if they examined the use of VLED, pharmacotherapies indicated for the treatment of obesity, or bariatric surgery of at least one weeks' duration in human participants of any age, and reported safety outcomes in people with severe or end-stage CKD (defined as eGFR <30 mL/min/1.73m^2 or on dialysis). Since liraglutide has regulatory approval for the treatment of obesity (at a dose of 3.0 mg daily), liraglutide studies in people with obesity were included regardless of dose and indication. Agents associated with weight loss but which do not have regulatory approval for obesity treatment (e.g. SGLT2 inhibitors, topiramate) were excluded. Single-dose pharmacotherapy studies, review articles, and published abstracts were excluded. No limits were placed on year of publication or language. Separate searches were performed for VLEDs, pharmacotherapy, and bariatric surgery. Search terms are given in **Table 2**.

Search results were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) and duplicates were removed. Two authors independently completed title and abstract and full-text screening and resolved conflicts via consensus by discussion at each stage. Additional papers were found from reference lists of original studies, review articles, and clinical practice guidelines via hand-searches. As we were aware of the limited quantitative data on this topic, particularly for non-surgical interventions, a formal systematic review and meta-analysis were not conducted.

Results

Very-low-energy diets

Searching of databases resulted in 51 citations, and hand-searching provided one additional article. After duplicates were removed, 46 papers remained. Title and abstract screening yielded 6 studies, of which only one full-text paper reported the use of a VLED in people with severe CKD and was included (**Figure 1**).

This was a pilot study examining the effect of a 12-week medically-supervised ketogenic VLED on parameters of kidney health in six participants (mean age 61 years, n=5 male) with obesity and advanced diabetic nephropathy.[15] Five participants had stage 4 CKD and one had stage 3B CKD, all had urine albumin excretion >30 mg/d and used an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. Participants expecting to require initiation of dialysis within nine months were excluded. The intervention comprised a VLED containing 800 kcal, at least 75g protein and less than 50g carbohydrate daily, along with recommendations for increased physical activity, and weekly physician review. The only adverse outcomes reported were transient elevations in blood urea nitrogen and serum creatinine at the beginning of the intervention in an unspecified number of patients, which resolved after reduction in the dose of antihypertensive medications. Overall, serum creatinine and cystatin C improved (reduced) over 12 weeks. Participants achieved a 12% reduction in

weight, representing a median weight loss of 14.2 kg (median BMI initial 38.6 vs week 12 34.0 kg/m^2, p=0.03).

Pharmacotherapy

Searching of databases found 323 citations, of which 308 remained after duplicates were removed. Title and abstract screening left 30 papers, of which 3 were reviewed (**Figure 2**). Details of these papers, and their findings, are summarised in **Table 3.** Two of the three pharmacotherapy papers examined the use of the subcutaneous GLP-1 receptor agonist liraglutide at a dose of 1.8 mg daily for the treatment of type 2 diabetes (T2D)[16, 17] and one reported the use of orlistat.[18] No studies that examined the use of other agents FDA-approved for the treatment of obesity (liraglutide 3.0 mg, phentermine, phentermine-topiramate, naltrexone-bupropion) met inclusion criteria.

Liraglutide

The studies in which liraglutide was used in people with T2D were one reporting outcomes of the large phase 3 LEADER randomised controlled trial (RCT),[19] and an RCT examining plasma liraglutide concentrations after 12 weeks of treatment[17].

The LEADER RCT compared liraglutide treatment for T2D with placebo for a mean of 3.8 years in 9340 participants with T2D and high cardiovascular risk, including 224 people with CKD stage 4 (eGFR 15 to <30 ml/min/1.73m^2) on a composite primary endpoint of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death. In people with eGFR <30 ml/min/1.73m^2, rates of adverse renal events were not different between liraglutide and placebo-treated participants, and the benefits of liraglutide on urinary albumin-to-creatinine ratio (ACR) and decline in eGFR showed similar patterns compared with the whole group.[19]

In an RCT of 20 participants on HD or peritoneal dialysis (PD) and 20 control participants with T2D treated 1:1 with liraglutide (up to 1.8mg daily) vs placebo, dose-corrected plasma trough liraglutide concentration at week 12 was 49% higher (95% confidence interval 6–109, P=0.02) in the ESKD group compared with the control group, with no indication of progressive accumulation of liraglutide in ESKD.[17] The study did not have adequate power for conclusions about clinical outcomes, but reported that nausea and vomiting were more common in liraglutide-treated participants with ESKD compared with normal kidney function, and tended to be transient in most (80%) participants with ESKD and all with normal kidney function (median [range] days of nausea 4 [86] in ESKD vs 0 [22] control). Appetite was reduced for a median [range] of 0 [83] days in the ESKD and 28 [83] days in the control group, and placebo-subtracted weight changes were -2.1 (-5.6 to 1.4) and -2.6 (-4.8 to -0.3) kg respectively.[17]

Orlistat

A prospective, open-label non-randomised study examined orlistat 120 mg three times daily in conjunction with a low fat 600 kcal deficit diet and exercise intervention for 24 months in 44 adults with CKD stage 3-5 compared with 20 control participants who declined to participate in the intervention.[18] All adverse effects were gastrointestinal disturbances, affecting 43% of the intervention group in the initial month of treatment, and 10% of participants at month 6. No participant withdrew due to adverse effects, there was no evidence of hyperoxalosis, and mean values for vitamins A and D, albumin, and international normalized ratio (INR) remained within normal limits throughout the study. Body weight differed in intervention and control groups between months 6 and 24, representing a difference from baseline in mean weight of approximately -8 kg (-8%) in the intervention and less than -1 kg (<-1%) in the control group at month 24. Nine of 26 (35%) from the intervention and one of 18 (6%) from the usual-care group who were otherwise eligible for kidney transplantation (apart from not meeting the BMI criterion of <30 kg/m^2 at baseline) were accepted for transplant listing.

Bariatric surgery

Screening of databases found 530 citations, of which 478 remained after duplicates were removed. Title and abstract screening left 111 papers, of which 24 were included in the qualitative synthesis (**Figure 3**). Characteristics of the included papers are summarised in **Table 4.** Only one study was prospective;[20] and most were retrospective cohort studies or analyses of electronic databases.

Outcomes following sleeve gastrectomy (SG) were reported in 20 studies,[20-39] gastric bypass (GB) in 17 studies,[21-25, 27-29, 32-35, 39-43] adjustable gastric banding (AGB) in 10 studies, [21-24, 27-29, 32, 41, 42] and duodenal switch in 2 studies.[24, 41] Fifteen studies reported on multiple bariatric surgery techniques.[21-25, 27-29, 32-35, 39, 41, 42]

Overall complication rates were low, though there was variability between studies (**Table 5**). Complication rates in people with ESKD did not differ from the control population in three studies,[22, 23, 38] but were higher in another three.[29, 33, 35] Of these, there was no increased complication risk in studies in which patients were matched for baseline comorbidities,[22, 38] but an increased risk in studies where the ESKD population had higher baseline comorbidities,[29, 33, 35] with pulmonary complications,[29, 35] infections,[35] and cardiac arrest[29] more commonly reported, though overall events were low. Laparoscopic Roux-en-Y gastric bypass was associated with a higher complication rate than SG or AGB in one retrospective electronic database analysis.[23] Nutritional parameters including ferritin, calcium and vitamin D did not differ from the control group in one study, with the exception of a lower serum vitamin B9 concentration in the ESKD group.[38]

Thirty-day mortality rate in the ESKD population was similar to controls in one retrospective analysis evaluating 234 individuals with dialysis-dependent CKD compared to a n=113,667 non-dialysis dependent control group (0.43% vs. 0.11%, p=0.13 [29]). However, 30-day mortality was higher in a retrospective study evaluating 801 patients with dialysis-dependent CKD compared to a control group

of 279,966 non-dialysis dependent individuals (RR 8.74, P<0.001),[35] and another comparing 917 patients with ESKD with 1:1 propensity score matching to a group without CKD (OR 11.59, p<0.001).[33] SG was more commonly performed in the ESKD population in all 3 studies. Individuals with ESKD were older and had a higher prevalence of comorbid medical conditions including hypertension, diabetes mellitus, ischaemic heart disease, and obstructive sleep apnoea in all studies.[29, 33]

Five-year mortality was significantly lower in a group of individuals who underwent bariatric surgery compared to a matched cohort of individuals with obesity and ESKD who did not undergo bariatric surgery (25.6% vs. 39.8%, HR 0.69 [95% confidence interval 0.60-0.78]).[24]

Weight loss outcomes are shown in **Table 5** and most were presented in terms of excess weight loss or BMI loss. Excess weight loss (EWL) ranged from 30-66% [20, 21, 25, 26, 31, 32, 34, 36-38, 40, 41] and BMI decreased by 6.5-9.8 kg/m^2.[26, 30, 31, 36] Compared to people with normal renal function, bariatric surgery was found to be as effective in those with ESKD in two studies [38, 39] but less effective in another (50 vs 73% EWL).[34] Baseline BMI was similar (39-42 kg/m^2) in these three studies, with SG performed in the majority of individuals in two studies,[34, 38] with gastric bypass more common in the other.[39] Total weight loss was stated in six studies, and ranged from 19-29%.[21, 25, 34, 36-38]

Discussion

There is a marked lack of data regarding the safety of intensive medical interventions for the treatment of obesity in people with severe or end-stage/dialysis-dependent CKD. There are relatively more reports of bariatric surgery, but prospective controlled studies are rare.

The available data on very-low-energy diets from one small (n=6) study indicate a need for careful clinical and biochemical monitoring in people with severe CKD. Short-term efficacy in people with stage 4 CKD and T2D,[15] with weight loss (12% body weight over 12 weeks) is comparable to results in

the general population with obesity.[44] Prospective studies in larger cohorts are required to confirm these findings and evaluate the safety and efficacy of longer-term use.

In the single study examining the use of an approved obesity medication in people with severe CKD,[18] participants with CKD, 50% of whom were dialysis-dependent, achieved and maintained a weight loss of ~8% after two years of orlistat in conjunction with a low-fat diet and exercise intervention. Orlistat is not systemically absorbed or renally excreted, therefore it is not surprising that the nature and frequency of adverse effects were in keeping with those in people without CKD.[45]

The GLP-1 analogue liraglutide is available in several countries for the treatment of both T2D (at a dose of up to 1.8 mg) and obesity (3.0 mg), and leads to dose-dependent weight loss. [46] It is thought to be endogenously metabolised without a specific organ as the primary route of elimination, although an early, sustained increase in trough plasma liraglutide concentrations during 12 weeks of treatment with 1.8 mg daily in dialysis-dependent people[17] suggests some renal elimination and/or degradation, which may limit use of the higher doses indicated for obesity treatment in this population.

The adverse effect profile of liraglutide appears similar in people with CKD compared with the general population, with a predominance of transient gastrointestinal side effects. In the RCT by Idorn et al[17] nausea and vomiting were more common and prolonged in liraglutide-treated dialysis-dependent participants compared with the normal kidney function group. This is in contrast to the findings of a post-hoc analysis of the LEADER trial, [47] although CKD in the latter analysis was defined as eGFR <60 (mean 46 ± 11) ml/min/1.73 m^2, and rates of gastrointestinal symptoms were not reported for people with severe and end-stage CKD. Rates of adverse renal events in the LEADER trial were not different between liraglutide and placebo-treated participants with eGFR <30 ml/min/1.73m^2,[19] and in people with T2D, liraglutide does not increase the risk of hypoglycaemia in those with severe/end-stage CKD compared with normal kidney function.[17, 48]

The weight-reducing effect of liraglutide $\leq$1.8 mg daily appears to be preserved in people with severe/end-stage CKD, although it should be noted that in these studies, liraglutide was being

examined as a treatment for T2D, rather than with a focus on weight reduction.[17] In liraglutide-treated participants in the LEADER study, weight loss was greater in those with eGFR <60 ml/min/1.73m^2 (mean [95% CI] -2.9 [-3.5 to -2.3] kg) than eGFR >60 (-2.1 [-2.4 to -1.8] kg) although not reported separately for the subgroup with eGFR <30 ml/min/1.73m^2.[48]

Importantly, in people with T2D and high cardiovascular risk, the benefits of treatment with liraglutide 1.8 mg daily on renal[19] and cardiovascular[48] outcomes extend to people with CKD stage 4, who comprised 2.4% (224/9430) of study participants. This is consistent with a retrospective evaluation of normal-weight patients with T2D that reported a slowing of annual decline in eGFR over up to 7 years' follow-up after initiation of liraglutide (up to 0.9 mg daily for at least 1 year), including in the 14% (81/568) of participants with baseline eGFR <15 and 15-30 ml/min/1.73m^2.[49] From the available data, it is not possible to make any conclusions about the use of liraglutide at a dose of 3.0 mg in people with ESKD.

Five other GLP-1 receptor agonists are currently approved by both the (U.S.) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of T2D but not obesity.[50-56]. The metabolic pathway for dulaglutide and albiglutide is presumed to be proteolytic degradation, [53, 54] whereas exenatide and lixisenatide are primarily eliminated by glomerular filtration [51, 52] and are therefore less suitable in the ESKD population.

The open-label randomised AWARD-7 trial, [57] which allocated 110 (29%) participants with stage 4 CKD and T2D to treatment with dulaglutide (0.75 or 1.5 mg weekly) over 12 months, found no difference in rates of serious adverse events in dulaglutide-treated vs comparator (insulin glargine) groups[57] in the overall study population, indicating that dulaglutide is likely to be safe in severe CKD, although outcomes were not presented separately for those with eGFR <30 ml/min/1.73m^2.

Glomerular filtration is not a major route of elimination for semaglutide,[56, 58] which is approved for T2D at a dose of up to 1.0 mg subcutaneously weekly, and in phase 3 studies for obesity treatment at a weekly subcutaneous dose of 2.4 mg. Recent data indicate that 0.5-1.0 mg weekly can safely be used

at eGFR <30 ml/min/1.73m^2 for up to 2 years. In the SUSTAIN 6 trial,[59] 95 of 3297 participants with T2D had CKD stage 4 (eGFR 15 to <30 ml/min/1.73m^2) and 12 had CKD stage 5 (eGFR <15 ml/min/1.73m^2). No significant differences compared to placebo were reported in rates of change in eGFR from baseline to week 104 in semaglutide-treated groups with stage 4 and 5 CKD. [60] Furthermore, there appeared to be no interaction of severe CKD with the beneficial effect of semaglutide on a composite cardiovascular outcome of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death (hazard ratio [95% CI] 0.73 [0.27-1.97] for eGFR<30 vs 0.74 [0.57-0.95] eGFR $\geqslant$ 30 ml/min/1.73m^2)[59]. The pharmacokinetics and safety profile of semaglutide co-formulated with the absorption enhancer sodium N-(8-[2-hydroxybenzoyl] amino) caprylate (SNAC) for oral administration[58] were not consistently affected by renal impairment or haemodialysis among patients with stage 4 CKD (n=12) or on haemodialysis (n=11) after 10 days of treatment.

The obesity medications phentermine, phentermine-topiramate and naltrexone-bupropion are all predominantly renally excreted. Pharmacokinetic studies show that exposure is approximately two-fold greater in people with severe CKD compared to normal renal function, and elevation in blood pressure is among their potential adverse effects,[10] making them less suited for the treatment of obesity in people with severe CKD in the absence of published data showing their safety in this population.

Bariatric surgery is increasingly being performed in people with CKD[23], with RCT evidence demonstrating remission of microalbuminuria (defined as early morning spot urine albumin/creatinine ratio <30 mg/g at 24 months after intervention) in 82% of participants with T2D and stage 1-3 CKD[61] after RYGB, compared with 48% after best medical treatment of diabetes.

While several analyses reported higher early complication rates in people with ESKD compared to those with normal renal function, it is notable that 5-year mortality was lower than in people with obesity and ESKD who had not undergone bariatric surgery. Discrepancies between studies could potentially be attributed to small sample sizes in several retrospective analyses. Thirty-day post-

operative mortality was higher than a non-CKD control group in one study, but it should be noted that patients with ESKD were older with a higher burden of comorbid disease.[33] Mortality rate in this study was not dissimilar to that observed in the general dialysis population, and lower than that reported for individuals with ESKD undergoing other non-emergent surgical procedures.[33] Lower rates of post-operative complications appear to support the use of sleeve gastrectomy (compared with gastric bypass) in the ESKD population,[23] but prospective, controlled studies are required to confirm this.

The available data, largely from retrospective cohort studies, indicate that in people with severe or end-stage CKD, bariatric surgery results in a mean total weight loss of 20-30%, equating to a BMI loss of around 6.5-10 kg/m^2. This degree of weight loss is comparable to that in the non-CKD population, and provides clear benefits of particular relevance to CKD, including reductions in glycaemia, blood pressure and albuminuria. However, the mean baseline BMI in bariatric surgery studies is often $\geq$45 kg/m^2, meaning that a BMI of $\leq$35-40 kg/m^2, required in many centres for eligibility to receive a kidney transplant, will not necessarily be achieved even with bariatric surgery.

Limitations and directions for future research

The limitations of the data available for review include the paucity of studies of intensive medical intervention for weight loss in people with severe or end-stage CKD, small participant numbers, and absence of long-term safety or efficacy data. Bariatric surgery studies are limited by a lack of prospective, controlled studies. These limitations highlight several areas where future research would be greatly informative. In particular, studies examining the effects of very-low-energy diets on body composition and kidney function, prospective controlled studies evaluating the efficacy and adverse effects of obesity pharmacotherapy, and comparative data on efficacy and safety outcomes of different bariatric procedures will be of value. Long-term studies evaluating endocrine and metabolic complications of bariatric surgery, such as hypoglycaemia, metabolic bone disease, and nutritional status are required in the ESKD population.

Conclusions

For people with severe or end-stage CKD and obesity who do not achieve therapeutic goals with standard lifestyle intervention alone, there are limited available data on which to base recommendations for additional obesity treatment strategies. Bariatric surgery appears to have an overall low rate of complications in people with severe CKD, and should be the treatment of choice if large weight loss (e.g. total weight loss $\geq$20%) is indicated, provided the appropriate technical expertise and facilities to manage this high-risk patient cohort are available. Very-low-energy diets can induce weight loss of 10-15% over ~3 months, but the current data are insufficient to recommend their use in people with ESKD and maintenance of weight loss is challenging. Addition of a GLP-1RA such as liraglutide, semaglutide or dulaglutide appears to be safe in people with ESKD at doses used for the treatment of type 2 diabetes, although their safety and efficacy at the higher doses registered (liraglutide) and under development (semaglutide) for obesity remain to be determined. Further prospective evaluation of intensive obesity management in the growing population with obesity and severe, end-stage and dialysis-dependent CKD are required as a matter of priority.

Author contributions

R.S., B.J.N and P.S. designed the study, R.S. conducted the initial literature search, R.S., B.J.N., H.H. and P.S. screened studies for inclusion, R.S. wrote the first draft of the manuscript, R.S., all authors revised the manuscript and approved the final version.

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Table 1. Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73m^2)
1	Kidney damage with normal kidney function	≥ 90
2	Kidney damage with mild decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Severely decreased GFR	15-29
5	Kidney failure	< 15 (or dialysis)

Table 2: Search terms

	VLED	Obesity pharmacotherapy	Bariatric Surgery
Ovid Medline	1. exp Caloric Restriction/ 2. exp Renal Insufficiency, Chronic/ 3. VLED.mp. 4. exp Diet, Reducing/ 5. exp Dialysis 6. 1 or 3 or 4 7. 2 or 5 8. 6 and 7	1. exp Renal Insufficiency, Chronic/ 2. exp Phentermine/ or exp Anti-Obesity Agents/ 3. exp Liraglutide/ 4. exp Orlistat/ 5. exp bupropion/ or exp naltrexone/ 6. exp Topiramate/ 7. 2 or 3 or 4 or 5 or 6 8. 1 and 7	1. exp Renal Insufficiency, Chronic/ 2. exp Bariatrics/ 3. exp Gastric Bypass/ or exp Gastrectomy/ 4. 2 or 3 5. 1 and 4
Ovid Embase	1. exp chronic kidney failure/ 2. exp end stage renal disease/ 3. exp dialysis/ 4. 1 or 2 or 3 5. exp low calorie diet/ or exp very low calorie diet 6. VLED.mp. 7. 5 or 6 8. 4 and 7	1. exp chronic kidney disease/ 2. exp end stage renal disease/ 3. 1 or 2 4. exp antiobesity agent/ 5. exp phentermine plus topiramate/ or exp phentermine/ 6. exp tetrahydrolipstatin/ 7. exp liraglutide/ 8. exp semaglutide/ 9. exp amfebutamone plus naltrexone/ 10. 4 or 5 or 6 or 7 or 8 or 9 11. 3 and 10	1. exp chronic kidney failure/ 2. exp end stage renal disease/ 3. exp bariatric surgery/ 4. exp sleeve gastrectomy/ 5. exp gastric bypass surgery/ 6. 3 or 4 or 5 7. 1 or 2 8. 6 and 7

Table 3: Obesity pharmacotherapy in ESKD

Reference	Design, location	Population	N (% women) I:C	BMI I;C	Mean eGFR (% on dialysis) I;C	Intervention	Follow up, drop-out (%) I,C	Weight change kg I;C	Adverse events n (%) I;C
Idorn 2016^ [17]	RCT Multicentre, Denmark	18-85y + T2D +HD or PD	14 (20); 10 (10)	31.6; 31.5	NR (100); NR (100)	Liraglutide 1.8 mg d, sc, 12 weeks vs placebo	12 weeks 36,0	-2.4; -0.2	819 (NR); 476 (NR)
Mann 2017^ [19]	RCT Multicentre, International	T2D + high CV risk	117 (NR); 107 (NR) (35% women in whole study population)	Whole population 32.5; 32.5	NR (0); NR (0)	Liraglutide 1.8 mg d, sc vs placebo	3.8 years NR	NR	Renal 22 (19); 23 (22)
MacLaughlin 2010 [18]	Open-label, prospective non-randomised, intervention Single centre, U.K.	18-75y + CKD + BMI>30 or BMI>28 + comorbidity	44 (39) 20 (35)	35.7 34.1	52 (50); 39 (55)	Orlistat 120mg tds, o + 600 kcal/d deficit diet + exercise vs usual care	24 months 27,0	-8.3; -0.7	3 (10) at 6m NR

^ only ESKD/severe CKD population shown; RCT, randomised controlled trial; I, intervention; C, control; T2D, type 2 diabetes; HD, haemodialysis; PD, peritoneal dialysis; NA, not applicable; NR, not reported; CV, cardiovascular; sc, subcutaneous; o, oral

Table 4: Bariatric surgery study characteristics

Reference	Design	Location, years	N (% women) I;C	Population	Age (mean) I;C	BMI (mean) I;C	eGFR (% on dialysis) I;C
Takata 2008 [40]	Retrospective case series	Single centre, US, 2004-2007	7(100)	ESKD on HD	46	50	NR (100)
Jamal 2015 [21]	Retrospective registry data	Single-centre, US 2006-2012	21 (43)	ESKD on dialysis	51	47.1	8.2(100)
Proczko 2019 [22]	Retrospective registry data	Single Centre, Poland, 2015-2019	19(74);19(53)	ESKD	45;42	43;44.2	NR(100);NR(0)
Modanlou 2009 [41]	Retrospective registry data	Medicare billing claims, US, 1991-2004	101(62)	ESKD Renal transplant candidates	44	38.1	NR
Sheetz 2019 [23]	Retrospective registry data	Medicare data, US, 2006-2016	2698 (58); 201679(26)		47;55	NR	NR
Yemini 2019 [25]	Retrospective cohort	Single Centre, Israel, 2009 - 2017	24(33)	Renal transplant candidate	54	41.5	NR;(71)
Alexander 2007 [43]	Retrospective cohort	Single centre, US, 1993-	41 (32 pre-transplant)	ESKD	44 (pre-transplant)	48 (pre-transplant)	NR
Maclaughlin 2012 [26]	Case series	Single Centre, UK, 2007-2010	9 (66)	5 HD, 1 CKD stage 4	44	44.2	(56)
Valle 2012 [42]	Retrospective case series	Single Centre, US, 2010-2011	5(60)	PD	41	43.3	(100)
Mozer 2015 [27]	Retrospective cohort	Multi-centre, US, 2006-2011	188 (53)	≥18y BMI ≥ 30	48	45.5	(18.4)
Saleh 2015 [28]	Retrospective cohort	Multi-centre, US, 2005-2011	667(36)	≥18y BMI ≥ 30	51	47.0	<30
Andalib 2016 [29]	Retrospective cohort study	Multi-centre, US, 2005-2013	234 (57)	Dialysis dependent CKD	47	47.0	(100)
Kienzl-Wagner 2017 [20]	Prospective non-randomized trial	Single centre, Austria	8(62)	Renal transplant candidates ESKD BMI ≥ 35	48	38.8	(100)
Kim 2017 [31]	Retrospective cohort study	Single Centre, US, 2011-2015	100 (59)	Transplant candidates. BMI ≥ 40 with ESKD	50	43.4	(85)
Al-Bahri 2017 [32]	Retrospective cohort	Single Centre, US, 1998 - 2016	16 (63)	ESKD on haemodialysis	54	48	(100)

Kim 2018 [30]	Retrospective cohort	Single centre, US, 2011-2016	20 (40)	BMI ≥40 or ≥35 with comorbidities . ESKD. transplant candidates	53	41.5	
Cohen 2019 [33]	Retrospective cohort	Multicentre, US, 2015-2016	925 (56)	≥18y ESKD on dialysis	49	44.7	(100)
Hansel 2019 [34]	Retrospective cohort	Multicentre, France, 2012-2015	17(38);17(38)	Stage 4-5 CKD	53;54	42;42	16(71);99(0)
Mazzei 2019 [35]	Retrospective matched cohort study	Multicentre, US, 2015-2016	801(55);279966(79)	Age > 18y	49;45	45.8;45.5	NR(100%);(0)
Bouchard 2020 [36]	Retrospective cohort	Single centre, Canada, 2013-2018	32(44)	BM I≥35 or WC≥110 cm CKD Stage 4 or 5	51	42.3	(91)
Kassam 2020 [37]	Retrospective Cohort	Single centre, US, 2011-2018	216(58)	Stage 4 CKD or ESKD. BMI ≥40	54	44.0	<30
Gaillard 2020 [38]	Retrospective cohort	Single centre, France, 2013-2018	29(52);87(64)	ESKD on dialysis BMI ≥35 Transplant candidates	52;50	39.3;39.6	(100)
Sheetz 2020 [24]	Retrospective registry data with matched cohort	Multicentre, US, 2006-2015	1597(56);4750(56)	ESKD on dialysis undergoing bariatric surgery ; non-surgical controls Age > 18y BMI ≥35	50;52	45.6;44.6	(100);(100)
Dobrzycka 2020 [39]	Retrospective matched pair analysis	Single Centre, Poland, 2015-2019	20(30);20(30)	ESKD with BMI ≥40 or ≥35 with comorbidities	42-64;42-64	42.8;43.6	<15(100);NR(0)

I, intervention; C, control; ESKD, end-stage kidney disease; NA, not applicable; NR, not reported; BMI, body mass index; HD, haemodialysis;

PD, peritoneal dialysis

Table 5: Bariatric surgery outcomes

Reference	Intervention	Follow up (m)	Weight loss (%) I;C	Complications (no. (%) with ≥1 AE)
Takata 2008 [40]	RYGB	15	61% EWL	0
Jamal 2015 [21]	18 RYGB 2 SG 1 LAGB	28	61% EWL (25% TWL)	33% Early: n=1 anastomotic leak, n=1 anastomotic stenosis Late: n=1 marginal ulcer, n=1 small bowel obstruction, n=1 cholecystitis, n=1 anastomotic stenosis
Proczko 2019 [22]	6 RYGB 11 OAGB 1 SG	1	NR	2 minor complications, 1 major complication (NS difference from non-ESKD group)
Modanlou 2009 [41]	65% RYGB 19% other GB 12% VBG 5% gastric restriction other than VBG or GB	NR	61% EWL	3.5% 30-day mortality
Sheetz 2019 [23]	84% SG 13% RYGB <1% AGB	NR	NR	SG: 3.4% (vs. 3.6% for non-ESKD group, p=NS) RYGB: 6.4% (vs. 6.2% for non-ESKD group, p=NS) AGB:2.5% (vs. 2.2% for non-ESKD group, p=NS)
Yemini 2019 [25]	17 SG 7 RYGB	47	66% EWL (27% TWL)	4% (n=1 mortality sleeve staple leakage)
Alexander 2007 [43]	GB	Variable	NR	0
Maclaughlin 2012 [26]	SG	9	43% EWL, BMI -8.4 kg/m^2	0% 30-day mortality Early: n=1 gastric leak, n=1 chest infection Late: n=1 fistula thrombosis, n=1 acute kidney injury, n=1 myocardial infarction
Valle 2012 [42]	1 AGB 4 RYGB	NR	NR	0
Mozer 2015 [27]	34% AGB 49% RYGB 17% SG	NR	NR	Mortality 0.7% Morbidity 5.8%
Saleh 2015 [28]	61% RYGB 30% AGB 10% SG	NR	NR	8.7% RYGB, 4.0% AGB, 7.8% SG N=1 30-day mortality
Andalib 2016 [29]	36% SG 43% RYGB 20% AGB 1% BPD-DS	NR	NR	Mortality 0.43% (vs. non-dialysis dependent 0.11%, p=0.134) Morbidity 5.98% (vs. non-dialysis dependent 2.31%, p<0.001)
Kienzl-Wagner 2017 [20]	SG	38	63% EBMIL	N=1 GORD, n=1 gastritis, n=1 dumping syndrome
Kim 2017 [31]	SG	12	30% EWL, BMI -6.5 kg/m^2	5% 90-day complications
Al-Bahri 2017 [32]	12 RYGB 3 AGB 1 SG	34	62% EWL	Zero 90-day complications
Kim 2018 [30]	SG	24	BMI -9.2 kg/m^2	Zero 90-day complications
Cohen 2019 [33]	16% RYGB 84% SG	NR	NR	30-day mortality 1.4% (OR 11.59 vs. non-ESKD control group)

Hansel 2019 [34]	94% SG 6% RYGB	12	50% EWL (20% TWL); 73% EWL (31% TWL)	N=1 acute hypertensive crisis, n=1 acute respiratory illness
Mazzei 2019 [35]	71% SG 29% RYGB	NR	NR	15% (RR 2.82 compared to non-dialysis group)
Bouchard 2020 [36]	SG	14	56% EWL, BMI -9.8 kg/m^2 (29% TWL)	3% 90-day complication, no major morbidity
Kassam 2020 [37]	SG	28	38% EWL (19% TWL) (198/243 patients with ESKD)	1.2%
Gaillard 2020 [38]	SG	12	58% EWL (21% TWL) ; 61% EWL (23% TWL)	14% 90-day complication (12% control group, P=NS)
Sheetz 2020 [24]	45% SG 42% RYGB 13% AGB 0.4% DS	36	NR	Lower 5-year all-cause mortality 26% (40% in matched group without surgery, HR 0.69 (0.60-0.78)
Dobrzycka 2020 [39]	45% GB 45% RYGB 10% SG	12	90% EBMIL; 68% EBMIL	N=1 surgical leak; n=0

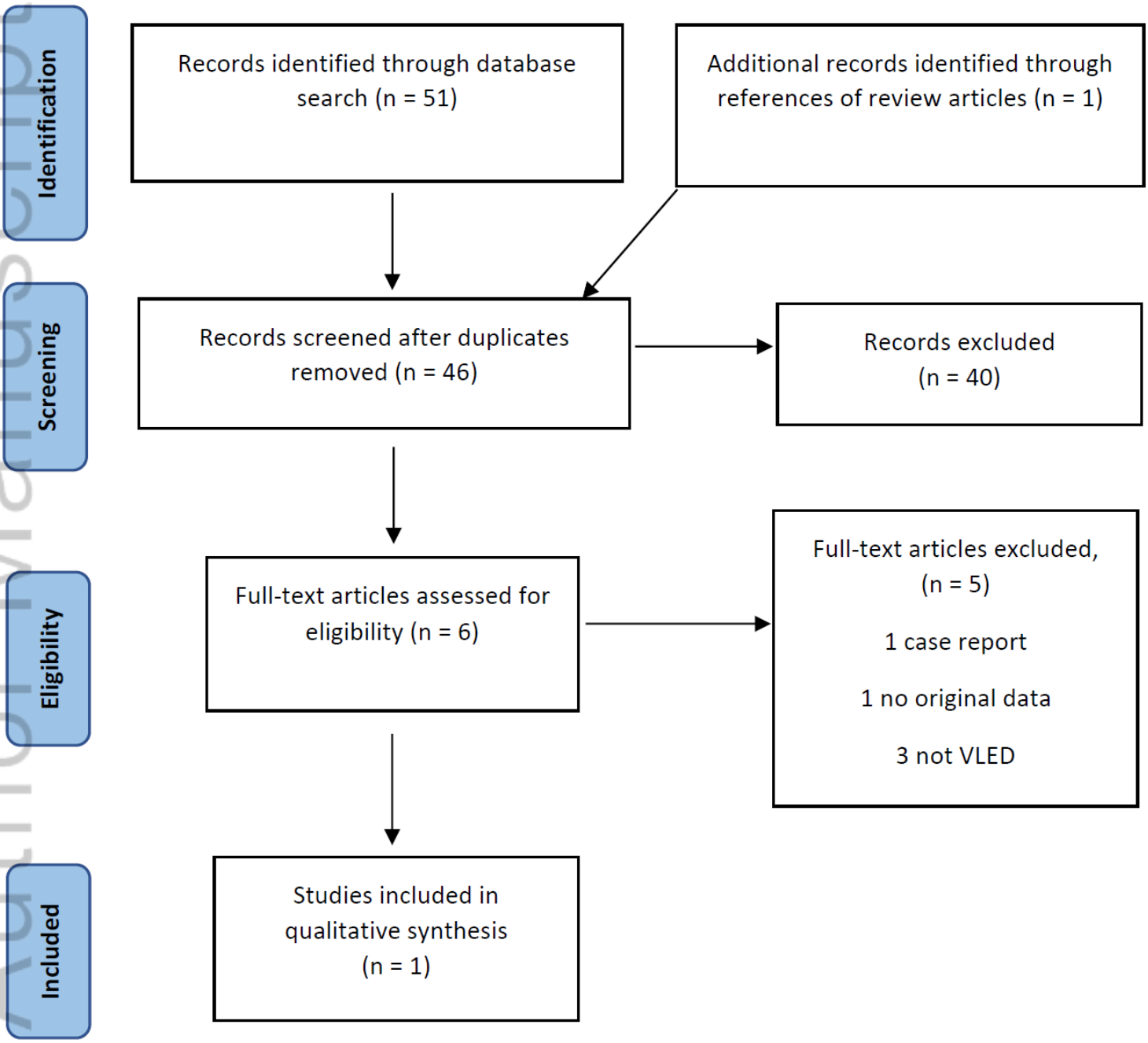
I, intervention; C, control; ESKD, end-stage kidney disease; NA, not applicable; NR, not reported; RR, relative risk; HR, hazard ratio, OR, odds ratio; EBMIL, excess body mass index loss, EWL, excess weight loss; TWL, total weight loss; SG, sleeve gastrectomy; RYGB, Roux-en-Y gastric bypass; GB, gastric bypass; AGB, adjustable gastric band; OAGB one-anastomosis gastric bypass; VBG, vertical banded gastroplasty; BPD, biliopancreatic diversion; DS, duodenal switch

Figure Legends:

Figure 1: Study search and selection for VLED studies

Figure 2: Study search and selection for pharmacotherapy studies

Figure 3: Study search and selection for bariatric surgery studies



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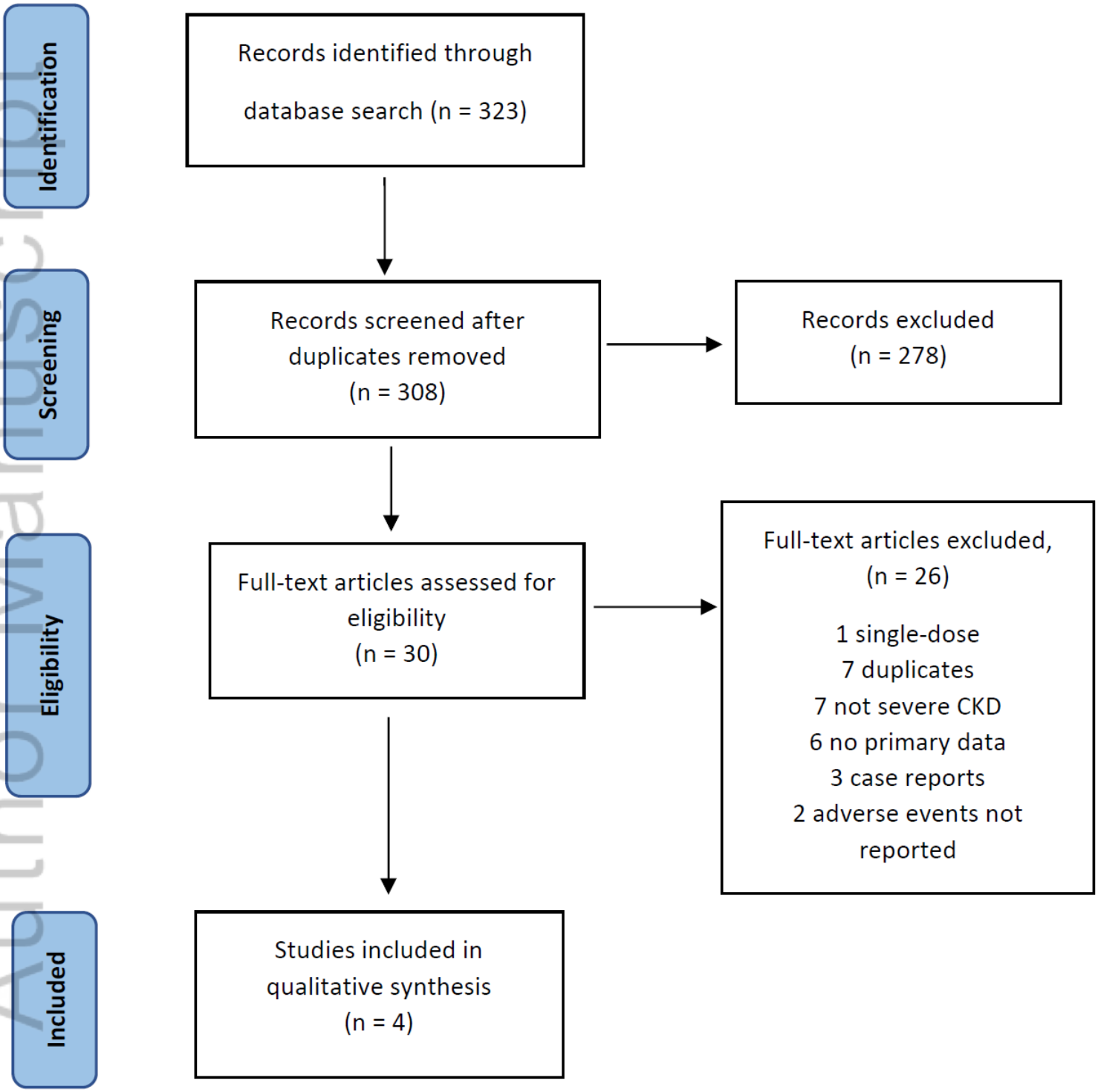

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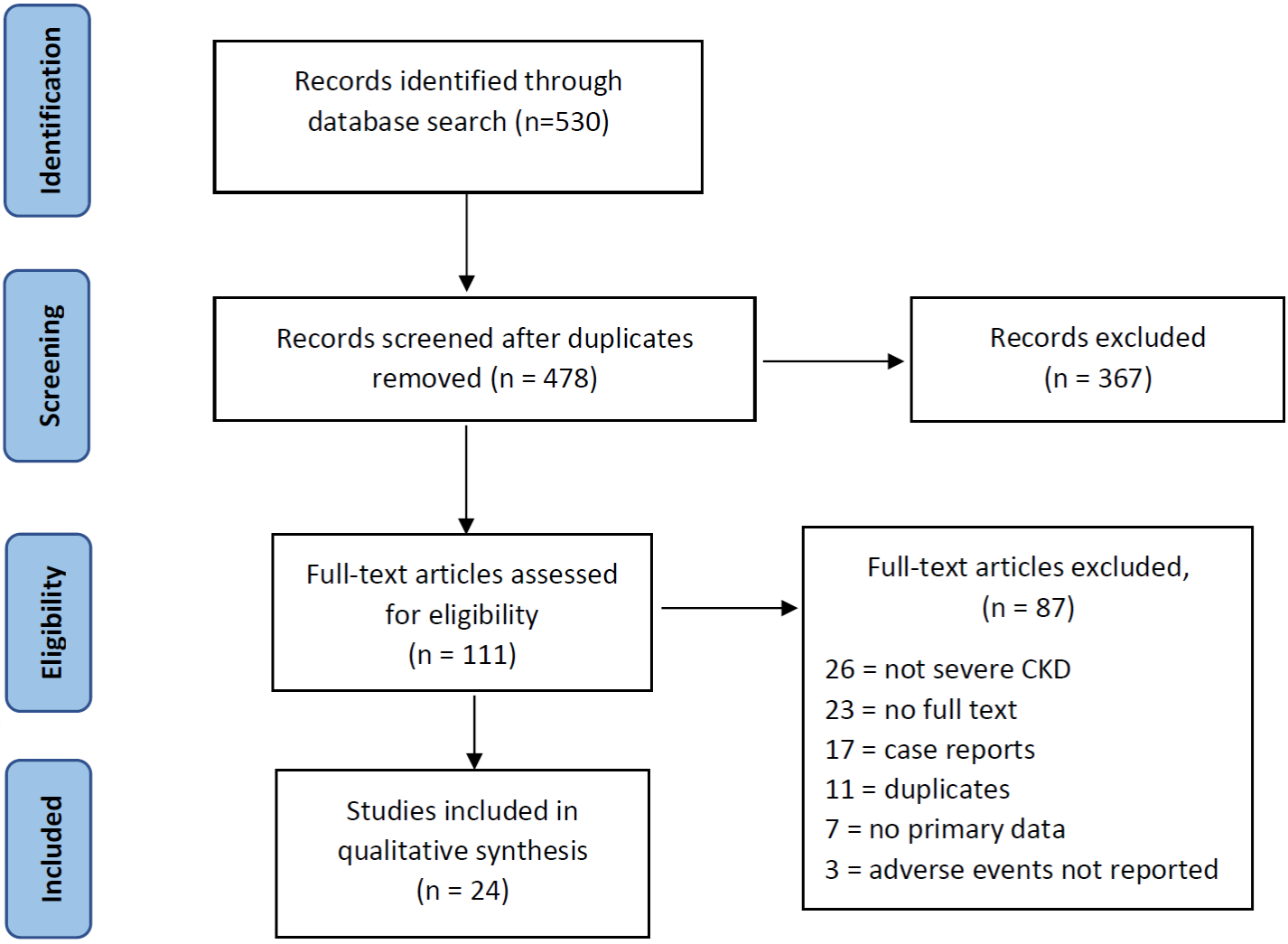

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