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Deintensification in older patients with type 2 diabetes: a systematic review of approaches, rates and outcomes

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Abstract

Background: Guideline bodies recommend less strict glycaemic targets in older people with diabetes. It is uncertain whether the benefits of deintensification or de-prescribing, commonly employed by clinicians to achieve the less strict targets, outweighs the harms in these patients. We conducted a systematic review of published evidence, to assess deintensification approaches and rates and evaluate the harms and benefits of deintensification with antidiabetic medication and other therapies amongst older people (≥ 65 years) with type 2 diabetes with or without cardiometabolic conditions.

Methods: We identified relevant studies in a literature search of MEDLINE, Embase, Web of Science, and Cochrane databases to 30 October 2018. Data was extracted on baseline characteristics, details on deintensification, and outcomes and was synthesized using a narrative approach.

Results: Ten studies (observational cohorts and interventional studies) with data on 26,558 patients with comorbidities were eligible. Deintensification approaches included complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication, but majority of studies were based on complete withdrawal or discontinuation of antihyperglycaemic medication. Rates of deintensification approaches ranged from 13.4% to 75%. Majority of studies reported no deterioration in HbA1c levels, hypoglycaemic episodes falls or hospitalisation on deintensification. On adverse events and mortality, no significant differences were observed between the comparison groups in the majority of studies.

Conclusion: Available but limited evidence suggests that the benefits of deintensification outweighs the harms in older people with type 2 diabetes with or without comorbidities. Given the heterogeneity of patients with diabetes, further research is warranted on which deintensification approaches are appropriate and beneficial for each specific patient population.

Keywords: Deintensification, deprescribing; medication; older adults; type 2 diabetes; cardiovascular disease; systematic review

Systematic review registration: PROSPERO 2018: CRD42018102853

Introduction

Type 2 diabetes is a chronic disease which is characterized by high levels of blood glucose (hyperglycaemia). It is one of the major causes of death globally.[1] Most patients with type 2 diabetes have at least one complication, which include cardiovascular disease (CVD), stroke, chronic kidney disease (CKD), retinopathy, and neuropathy.[2] Cardiovascular complications are the leading cause of morbidity and death in these patients.[1]

The major goal of managing type 2 diabetes is to achieve appropriate reduction in glucose levels, in order to minimize the risk of complications, which include adverse vascular events.[3] To achieve appropriate glycaemic targets as set by guideline bodies, antihyperglycaemic medications are usually initiated individually or in combination [4] in a timely manner when appropriate to prevent therapeutic inertia defined as the failure to advance treatment by a healthcare professional when appropriate to do so.[5] At the same time, there needs to be a balance between the relative risks of clinical inertia (i.e., the failure to deintensify therapy when appropriate to do so) versus overtreatment in the management of glycaemia in patients with diabetes.[6] In older patients with type 2 diabetes, achieving glycaemic control is very problematic; with adverse effects such as hypoglycaemia reported to be common in such patients.[7,8] Consequencies of hypoglycaemia impacts substantially on patients and the healthcare system – these include physical injury, psychological harm, impaired cognition, reduced quality of life, mortality, additional manpower and resource utilization and costs of providing emergency assistance.[9-14] Majority of older type 2 diabetes patients have co-existing frailty and comorbidities such as renal and cognitive impairment and the risk of hypoglycaemia is particularly high in these patients.[7,9,15] Despite recommendations by guideline bodies to individualise glycaemic targets with risk assessments aimed at avoiding overtreatment and hypogycaemia,[16-18] recent data suggest increased hospital emergencies for hypoglycaemia.[19] Indeed, evidence suggests that older people with complex multiple comorbidities are being overtreated with drugs that cause hypoglycaemia.[20-22] Though some evidence suggests the adverse effects of overtreatment with antihyperglycaemic drugs

in older patients outweigh the benefits,[20] data on the potential benefits and harms of stopping, reducing, or substituting these antihyperglycaemic agents (i.e., deintensification) in the older patients with type 2 diabetes and comorbidities remains uncertain. Deintensification as defined by a position statement from Primary Care Diabetes Europe, is the de-escalation or down-titration of glucose-lowering therapy by reducing the dose, deprescribing or substituting one agent for a less potent glucose-lowering therapy.[23] Deintensification also includes deprescribing, which is the process of withdrawal or stopping inappropriate medication and the ultimate goal is improving outcomes and managing polypharmacy.[24,25] Deintensification approaches are on the increase and it is becoming an established part of the prescribing process, especially in the management of older patients with multiple comorbidities.[26,27] There is emerging evidence on the efficacy of deintensification from several randomised trials and observational studies conducted in other patient populations.[25] In older patients with type 2 diabetes with or without comorbidities, it is uncertain whether the benefits of deintensification outweighs the harms in these patients. In this context, using a systematic review of all available published observational and interventional evidence, our primary aim was to assess deintensification approaches and rates and evaluate the harms and benefits of deintensification with antidiabetic medication and other therapies amongst older people (≥ 65 years) with type 2 diabetes with or without other cardiometabolic conditions such as CVD, CKD, or dementia. Given that majority of these patients are also on non-diabetic medication (e.g., lipid lowering drugs, antihypertensives) for their comorbidities, we also included these medications in our evaluation. We also sought to explore if there are gaps in the existing evidence.

Methods

Eligibility criteria

A predefined protocol was used to conduct this review and also in accordance with PRISMA and MOOSE guidelines [28,29] (**Appendix 1-2**) and using a protocol, which has been registered in the PROSPERO prospective register of systematic reviews (CRD42018102853). We searched for

observational (cross-sectional, prospective or retrospective case control, prospective cohort, retrospective cohort, case-cohort, or nested-case control) studies and clinical trials (randomised controlled trials (RCTs) including cluster and pragmatic trials and non-randomised controlled trials) that had reported on (i) older patients (≥ 65 years) with type 2 diabetes with or without co-existing cardiometabolic conditions such as CVD, CKD, or dementia who were taking antidiabetic medication with or without other therapies for their conditions; (ii) reported deintensification approaches (stopping drug treatment entirely, reducing dose, gradual tapering, or substitution); and/or (iii) reported outcomes such as measures of glycaemia, admission rates, hospitalisations, complications, mortality, quality of life, and patient satisfaction. The age cut off applied if the average age of study participants age was 65 years or older; more than 75% of study participants were aged 65 years and older; or ability to extract data on participants aged 65 years and older from the study. The following exclusions were applied (i) studies not reporting deintensification approaches; (ii) those not including patients with type 2 diabetes; (iii) those including patients < 65 years; or (iv) studies that included only terminal or palliative patients.

Definition of terms

Based on the PICO (Population, Intervention, Comparator, and Outcome) framework, the population included older patients (≥ 65 years) with type 2 diabetes with or without co-existing cardiometabolic conditions such as CVD, CKD, or dementia, who were taking antidiabetic medication with or without other therapies for their conditions. The intervention was a deintensification rate, defined as the proportion of patients for whom one medication was stopped, reduced, or switched [(n/N)*100], where n denotes number of patients stopping, reducing, or switching medication and N refers to the total number of patients. The comparator included usual care or continuing medications. Outcomes included measures of glycaemia, admission rates, hospitalisations, complications, mortality, quality of life, and patient satisfaction.

Data sources and search strategy

We searched MEDLINE, Embase, Web of Science, and Cochrane databases from inception to October 2018. The computer-based searches combined free and MeSH search terms and combination of key words related to diabetes and other cardiometabolic conditions (e.g., "diabetes mellitus", "hypertension"); older patients ("aged", "ageing", "geriatric"); medication (e.g., "prescription", "antidiabetic", "hyperglycaemic"); and deintensification (e.g., "deprescribe", "discontinue", "deintensify" "cessation"). There were no restrictions on language. Reference lists of retrieved articles were manually scanned for all relevant additional studies and review articles missed by the original search. Full details on the search strategy are presented in **Appendix 3**.

Data extraction and quality assessment

One reviewer (S.K.K.) independently extracted data and performed quality assessments using a standardized predesigned data collection form. A second reviewer (S.S.) checked extracted data with that in the original articles. The titles and abstracts of all articles identified by the broad literature search were assessed independently by two reviewers (SS and SKK). Studies that did not meet the inclusion criteria were discarded. Full text of selected articles were retrieved and assessed to determine if the met the inclusion criteria. Those studies which met the inclusion were included in the review and the data were extracted independently by two reviewers (SS and SKK) using standard data extraction form. The quality of the studies were assessed independently by both reviewers.

Data was extracted on study, publication date, geographical location, study design, mean age, percentage of males, duration of follow-up, sample size, comorbidities, concomitant medications, doses, frequency, duration, deintensification approach (stopping/tapering/switching), and data/risk estimates on benefits and harms of deintensification. Each article was assessed using the inclusion criteria and any disagreement regarding eligibility of an article was discussed, and agreement reached by consensus with a third reviewer. Additionally, in the case of multiple publications, data on the study with the most up-to-date or comprehensive information was extracted. Methodological quality

of observational cohort studies was assessed based on the nine-star Newcastle–Ottawa Scale (NOS),[30] a validated tool for assessing the quality of non-randomised studies, including cohort and case-control studies. It uses three pre-defined domains namely: selection of participants (population representativeness), comparability (adjustment for confounders), and ascertainment of outcomes of interest. The NOS assigns a maximum of four points for selection, two points for comparability, and three points for outcome. Nine points on the NOS reflects the highest study quality. For cross-sectional studies, we assessed quality using the NOS modified for cross-sectional studies (**Appendix 4**[31]). A maximum score of 8 reflected the highest study quality.

Statistical analysis

The characteristics of the deintensification approaches and outcomes reported for each study were summarized in tables and narrative synthesis was performed.

Patient and Public Involvement

The study was supported by a patient focus group which provided input to the programme of research on the 9th of April 2018. Patients partnered with us for the design to refine the population to include other multimorbidities instead of just diabetes. They suggested that the burden of deintensification or deprescribing could not just be worsening of glycaemic control but admissions and falls. It is our intention to continue to engage the group for the dissemination of the findings

Results

Study identification and selection

Figure 1 shows the flow of studies through the review. The literature search identified 8,547 potentially relevant citations. After the initial screen based on titles and abstracts, 59 articles were selected for full text evaluation. Following detailed assessment of the full articles, 49 were excluded because (i) populations were not relevant to review (n=28); (ii) the intervention was not relevant

(n=16); (iii) outcomes not relevant to review (n=3); (iv) one article used the same population sample as another study included in the review; and (v) one was a review article. The remaining 10 articles based on 10 unique studies met the inclusion criteria and were included in the review.[32-41]

Study characteristics and study quality

Table 1 summarises the key baseline characteristics of the included studies. Studies were published between 2008 and 2017. Overall, the studies involved 26,558 unique participants with type 2 diabetes. The majority of studies (n=3) were conducted in Europe (Sweden, and UK); three in the United States; and three in Asia (Japan). One study was conducted in 20 countries in Asia, Australasia, Europe, and North America. Only one study, with 98 patients with diabetes, was based on patients in Nursing Homes.[32] The mean/median baseline age of participants ranged from 65.8 to 86.5 years. Study designs comprised of prospective cohorts (n=2); retrospective cohorts (n=2); observational cohorts with controls (n=2); case series (n=2); post-hoc observational analysis of a RCT (n=1); and cross-sectional retrospective sub-analysis of a RCT (n=1). No RCT was identified. Sample size of studies ranged from 5 to 11,140 participants. The average follow-up durations for studies providing data ranged from 3 months to 4.3 years; however, for the majority of studies, it ranged from 3 to 6 months. Study populations comprised older patients with type 2 diabetes with comorbidities such as coronary heart disease (CHD) and kidney dysfunction and were on antihyperglycemic medication as well as blood pressure medication. Among the observational cohort studies, quality score using NOS ranged from 3 to 8 and that for the cross-sectional study was 4 (**Appendix 5**).

Deintensification approaches and rates

It was planned to synthesise risk ratios for dichotomous outcome data and mean differences for continuous outcomes if consistent outcomes were reported for multiple studies; however, given the limited number of studies, type of measures reported, and the diversity of the study designs and

populations, a formal meta-analysis could not be performed. We could also not make effective comparisons across studies because of the heterogeneity of the data.

Table 2 provides details of the deintensification approaches and outcomes reported by each eligible study. The approaches varied and included complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication. However, majority of studies reported on complete withdrawal or discontinuation of therapy. The main reasons for considering deintensification was tight glycaemic control and being at risk of hypoglycaemia, which was reported by five studies.[32,34-36,38] One study reported on the potential for deprescribing in care home residents with type 2 diabetes using a medicines optimisation tool, which was validated by a care home physician;[39] though the actual deprescribing was not performed and evaluated in the study, we included it in this review because of its relevance to the topic. Except for one study which was based on blood pressure lowering therapy,[40] the most common medications that were deintensified were antihyperglycaemic agents comprising of sulfonylureas, alpha-glucosidase inhibitors, dipeptidyl peptidase 4 inhibitors, and insulin. The majority of studies were before and after study designs and four studies compared deintensification approaches to usual care.[32-34,40] Lipska and colleagues examined the frequency of discontinuation of antihyperglycemic agents on discharge among patients with diabetes admitted for acute myocardial infarction on a diabetic regimen;[33] of 8751 patients admitted on at least 1 antihyperglycemic agent, 1170 (13.4%) were discharged off antihyperglycemic therapy. In a pilot study to examine the efficacy and safety of switching from subcutaneous injection of insulin to oral administration of vildagliptin in 20 patients with type 2 diabetes undergoing hemodialysis, 11 (55%) of patients switched successfully.[38] In a study that investigated the withdrawal of all antihyperglycemics or reduction in insulin versus no change in diabetes medication in Swedish nursing home patients, withdrawal of the diabetic medication was successful in 24 (75%) patients 3 months after drug discontinuation.[32] In the study that reported on the potential for deprescribing in care home residents with type 2 diabetes using the NHS PrescQIPP document

'Optimising Safe and Appropriate Medicine Use' (OSAMU) (now replaced by the Improving Medicines and Polypharmacy Appropriateness Clinical Tool (IMPACT)[42]) an evidence-based tool developed to allow for appropriately stopping or continuing medicines in end of life; of the 67 potentially inappropriate medications, a physician agreed that 26 (38.8%) of these could be discontinued without further question.[39]

Glycaemic control

Seven studies reported outcomes of glycaemic control after deintensification approaches (**Table 2**). In two studies that compared discontinuation or reduction in dose of antihyperglycemic medication with usual care, no significant differences were found in HbA1c levels.[32,34] In one study,[34] there was no significant difference in hypoglycaemia rates between the groups post-intervention. In eight patients who had their hypoglycaemic medications completely withdrawn over 3-6 months and followed up for a year, there was no significant difference between the mean HbA1c at the point of hypoglycaemic medications withdrawal and at 1 year of follow-up.[36] Switching α-glucosidase inhibitors from acarbose or voglibose to miglitol did not affect levels of HbA1c and fasting glucose in 35 Japanese patients; in addition, glucose fluctuations improved on switching.[37] In 5 patients with type 2 diabetes and on haemodialysis, discontinuation of insulin and other oral hypoglycaemic agents and switching to liraglutide caused reduction in levels of HbA1c and hypoglycaemic episodes.[41] In a retrospective analysis of veterans converted from glyburide to glipizide, mean HbA1c levels increased by 0.34% 1 year after conversion; however, there was a significant reduction in hypoglycaemic events.[35]

Other beneficial and adverse outcomes

In two studies that evaluated switching from one antihyperglycaemic agent to another, no adverse events were recorded in both studies.[37,38] In a study comparing patients whose antihyperglycaemic therapy was discontinued on discharge versus those discharged on antihyperglycaemic therapy in Medicare beneficiaries admitted on diabetes medication, rates of readmissions did not differ

significantly between the two groups.[33] In a post-hoc observational analysis of an RCT of blood pressure lowering and intensive glucose control in patients with type 2 diabetes, permanent discontinuation of blood pressure lowering medication during the study period compared to continuing administration of randomised medications was associated with increased risk of macro- and micro-vascular events.[40] When insulin and other oral hypoglycaemic medications were switched to liraglutide in five patients on haemodialysis, there was improved quality of life in more than half of the patients.[41]

Mortality

Three studies reported mortality outcomes after deintensification approaches (**Table 2**). Two studies reported that discontinuation of antihyperglycaemic or blood pressure lowering therapy was associated with an increased risk of mortality.[33,40] In the study by Sjoblom and colleagues, which compared complete withdrawal or reduction in dose of antihyperglycemic medication with usual care, there was no significant difference in the risk of mortality for the deintensification group compared to the non-intervention group.[32]

Discussion

Key findings

Using a systematic review, we have assessed deintensification approaches and rates and the associated benefits and harms from available published observational and interventional studies conducted in older people with type 2 diabetes, including those with comorbidities such as CHD, hypertension, and kidney disease. Deintensification approaches identified included complete withdrawal, discontinuation, reducing dosage, conversion, or substitution of at least one medication; however, majority of studies were based on complete withdrawal or discontinuation of antihyperglycaemic medication. Deintensification rates varied based on the approach but generally ranged from 13.4% to 75%. For studies reporting relevant data on glycaemic control after deintensification, majority

reported no deterioration in HbA1c levels or hypoglycaemic episodes in the patient populations. On adverse events and mortality, no significant differences were observed between the comparison groups in the majority of studies.

Comparison with previous studies

We identified only one systematic review which attempted to synthesize evidence on studies evaluating the effects of deprescribing versus continuing antihyperglycemics in older adults with type 2 diabetes. Black and colleagues included only two studies in their review and concluded that there was limited and low-quality evidence on deprescribing antihyperglycaemic medications.[43] We have adopted a broader approach which involved assessing deintensification approaches and their benefits and harms in older patients with type 2 diabetes with or without comorbidities. Indeed, the evidence is limited and of low quality, but based on the available evidence, our findings show that deintensification may be feasible and its benefits generally outweigh the harms. We have also identified some gaps in the evidence. None of the studies provided specific guidance on how patients were identified for the deintensification approach; however, a few studies reported considering deintensification based on patients with tight glycaemic control or at high risk for hypoglycaemia. Though one of the included studies did not specifically evaluate a deintensification approach, the authors assessed and validated a medicines optimisation tool which was found to be appropriate in allowing pharmacists to identify medicines eligible for deprescribing in care home residents with type 2 diabetes, thus reducing polypharmacy and potentially adverse events.[39] Finally, though discontinuation of therapy was the most common deintensification approach reported, it was difficult to conclude from the findings that a particular approach was associated with more benefits.

Implications of findings

For several decades, clinical practice guidelines for glycaemic control have focused on intensifying therapy to achieve target levels of risk factors, such as reducing HbA1c levels to less than 7.0%.[44,45]

However, it appears this overtreatment or treatment intensification is not harmless or associated with more benefits. A number of RCTs have shown that intensive glycaemic control directed at lower HbA1c targets are associated with only minor cardiovascular benefits but increased adverse events such as mortality.[46] Evidence shows that older people with type 2 diabetes and other comorbidities are being overtreated with drugs that cause hypoglycaemia.[20-22,47] Hambling and colleagues observed that older people, including those with comorbidities such as CKD or dementia, were managed to similar intensive thresholds as those without CKD or dementia.[47] These elderly patients are especially vulnerable to hypoglycaemic episodes and other adverse events such as fractures, head injuries, CVD, or even death;[9,11,12] given predisposing factors such as advanced age, frailty, long duration of diabetes, polypharmacy, and comorbidities such as CKD and cognitive impairment.[9,15,48,49] Intensive treatment with antihyperglycaemic medication in these patients doubles the risk of hypoglycaemia.[50] In addition, only few older patients with type 2 diabetes and complex comorbidities actually gain substantial benefit from intensive management.[51,52] The need for deintensification approaches is therefore of substantial relevance in healthcare. Indeed, deintensification or deprescribing is already becoming an essential part of prescribing when managing patients with multiple conditions and end of life.[26,27,53] Available evidence from our review suggests that deintensification is associated with more benefits than harms and it is feasible. However, though discontinuation or complete withdrawal of antihyperglycaemic therapy is very commonly used, it is uncertain if it is associated with more benefits compared with other approaches. Furthermore, guidance is needed on how to identify patients for deintensification and which approaches will be suitable for a particular patient.

Strengths and limitations

Some strengths and limitations of this study merit careful consideration. Compared to the only relevant previous review which only evaluated the effects of deprescribing antihyperglycaemic medications in older adults with type 2 diabetes,[43] our review was more detailed and focussed on deintensification in patients with or with comorbidities. Our literature search was detailed and spanned multiple databases, yielding 10 articles on the topic. There were a number of limitations, but

majority were inherent to the included studies and not the actual review. The data was sparse and heterogenous, hence we were unable to pool data as originally planned in our published protocol (CRD42018102853); however, we were able to summarise the evidence according to identified consistent themes. We included a diversity of study designs such as observational cohorts, case series, and post-hoc observational analysis of RCTs, and these were generally not of high methodological quality. Majority of studies were of short follow-up durations of a few months, which precludes inadequate evaluation of the impact of an intervention. Furthermore, studies selectively reported outcomes and did not report results in a manner that could assist clinicians in making decisions. Given these limitations, the findings should be interpreted with caution.

In conclusion, available but limited evidence based on mixed study designs suggest that the benefits of deintensification outweighs the harms in older people with type 2 diabetes with or without comorbidities. The data also suggests deprescribing is feasible. There are still some unanswered questions. There is limited information to guide which deprescribing approaches to use in order to achieve safe individual targets in older patients. The appropriate glycaemic control targets in such patients are also uncertain. Guideline bodies have started to recognise the harms of overtreatment in older patients with diabetes and several recommendations have been made to reflect the heterogeneity of these patients. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) guidelines for diabetes treatment recommend an individualised approach based on the preference of the patient, comorbidities, severity of diabetes-related complications, and life expectancy.[44] In recent guidelines, the ADA, the American Geriatrics Society, and the American Board of Internal Medicine's Choosing Wisely campaign recommend target HbA1c levels of 7.5% or 8.0% for older patients and those with limited life expectancy.[54-56] Given the heterogeneity of patients with diabetes, further research is warranted on which deintensification approaches are appropriate and beneficial for each specific patient populations.

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Figure legends

Figure 1. Selection of studies included in the review

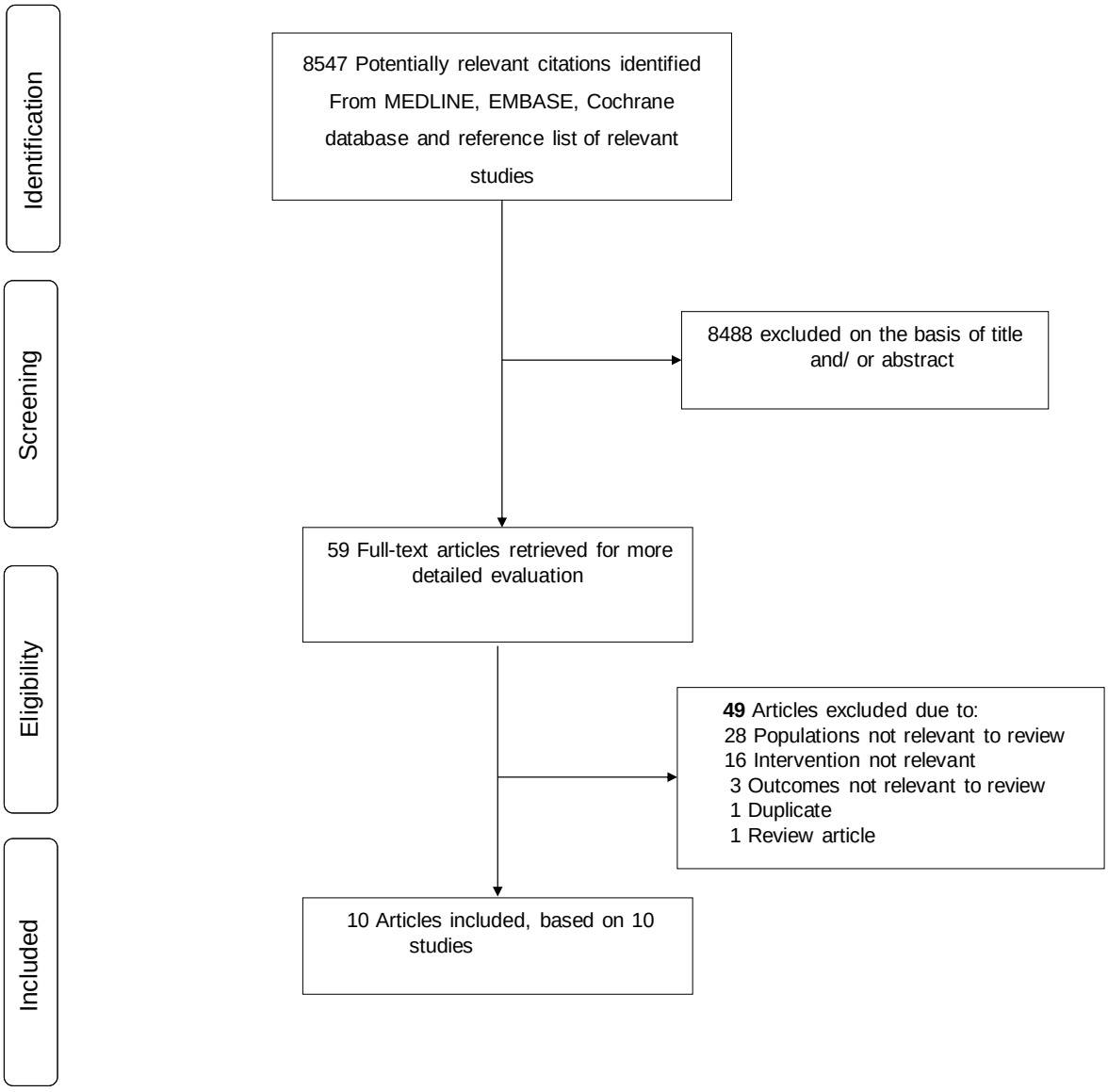

Table 1. Baseline characteristics of studies included in review

Lead Author, Publication Date	Name of study (Population source)	Location	Study design	Baseline population	Year of baseline survey	Baseline mean/median age (years)	% male	Average follow up	Total participants	Study quality
Sjoblom, 2008	NR (Nursing homes)	Sweden	Prospective cohort with controls	Elderly patients with T2DM with HbA1c ≤ 6.0%	2006	84.1	41.8	6 months	98	4
Lipska, 2010	NHCP (Medicare beneficiaries)	USA	Retrospective cohort	Older patients with diabetes after AMIs and on at least 1 antihyperglycaemic agent	1998-2001	76.5	47.2	1 year	8751	8
Aspinall, 2011	Veteran Affairs Database	USA	Retrospective cohort with controls	Community dwelling veterans	2007-2008	77.0	99.5	5 months	6254	7
Skoff, 2011	VHA	USA	Retrospective cohort	Elderly diabetes veterans with renal dysfunction	2008-2010	74.0	99.3	1 year	141	5
Abdelhafiz, 2014	NR (Outpatient health clinic)	UK	Case series	Older patients with diabetes	NR	86.5	25	1 year	8	NA
Hariya, 2014	NR (Healthcare setting)	Japan	Prospective cohort study	Patients with T2DM	2007-2008	65.8	48.6	3 months	35	3
Yoshida, 2016	NR (Healthcare setting)	Japan	Prospective cohort study	Patients with T2DM on haemodialysis	2010-2011	66.0	55.0	24 weeks	20	3
Andreassen, 2016	CAREMED (clinical trial)	UK	Cross-sectional retrospective sub-analysis of a RCT	Elderly patients with T2DM	NR	86.0	51.4	NA	106	4
Hirakawa, 2016	ADVANCE	20 countries	Post-hoc observational analysis of RCT	Patients with T2DM on blood pressure lowering and intensive glucose control	2001-2003	65.8	57.5	4.3 years	11,140	8
Kondo, 2017	NR (Healthcare setting)	Japan	Case series	Patients with T2DM on haemodialysis	2011-2012	67.6	80.0	3 months	5	NA

AMI, acute myocardial infarction; CHD, coronary heart disease; LDL-C, low density lipoprotein cholesterol; NA, not applicable; NHCP, National Heart Care Project; NR, not reported; RCT, randomised controlled trial; T2DM, type 2 diabetes mellitus; VHA, Veteran's Health Administration

Table 2. Deintensification approaches and outcomes in eligible studies

Lead Author, Publication Date	Selection of patients for deintensification	Deintensification approach and description	Comparison/control	Intervention/control	Deintensification rate	Glycaemic control	Other outcomes and adverse effects	Mortality
Sjoblom, 2008	Patients with HbA1c ≤ 6.0% and on antidiabetic drugs or insulin, or both in combination, were invited to participate in the diabetes medication withdrawal	Plasma glucose was measured on 3 consecutive days before medication withdrawal. Complete withdrawal of oral anti-diabetic drugs, complete insulin withdrawal when doses were 20 units/day and reduced by half in patients on more than 20 units/day	No change in diabetes medication	32 / 66	Withdrawal of the diabetic medication was successful in 24 (75%) patients 3 months after drug discontinuation	HbA1c levels: 5.8% (Intervention arm): 6.6% (Control arm) at 6 months		5 out of 32 patients (16%) in deprescribing group compared to 14 out of 66 (21%) in the non-intervention group died: 0.74 (0.29-1.87)
Lipska, 2010	Reasons behind the discontinuation of antihyperglycemic therapy was not evaluated	Discontinuation of antihyperglycemic agents on discharge. Was based on retrospective analysis of a database	Discharged on antihyperglycemic therapy	1170 / 7581	13.4% discharged off antihyperglycemic therapy	NR	Readmissions did not differ between the two groups	Discontinuation of therapy was associated with HR (95% CI) of 1-year mortality of 1.29 (1.15-1.45)
Aspinall, 2011	Patients considered at increased risk of hypoglycaemia – were on glyburide with a calculated creatinine clearance of < 50 ml/min	Discontinuation of glyburide. Information regarding risk of hypoglycaemia in older persons on glyburide and instructions for switching to alternative agent provided to pharmacists, who could then contact patients' physicians to deprescribe	Received usual care	4368 / 1886	During the study period, glyburide was discontinued in 71.5% (3123/4368) of the patients in the targeted cohort and in 56.0% (1057/1886) of the nontargeted cohort.	No significant difference in HbA1c levels was found between the group of patients who discontinued glyburide and those who continued taking this medication. No significant difference was observed in the rates of hypoglycaemia post-intervention between the intervention and control groups	NR	NR
Skoff, 2011	Patients considered at increased risk of hypoglycaemia – were on glyburide with renal dysfunction	Conversion from glyburide to glipizide	NA	NA	NA	Increase in HbA1c level of 0.34% at 1 year after conversion. Hypoglycaemia was confirmed in 44 (31.2%) patients during glyburide treatment and in 18 (12.8%) patients during treatment with glipizide	Liver and renal functions were similar at the point of medication withdrawal compared with their levels at the point of introducing diabetes treatment	NR

Lead Author, Publication Date	Selection of patients for deintensification	Deintensification approach and description	Comparison/control	Intervention/control	Deintensification rate	Glycaemic control	Other outcomes and adverse effects	Mortality
Abdelhafiz, 2014	Tight glycaemic control (HbA1c ≤ 6%) was the main reason for medication withdrawal in two patients, while recurrent episodes of hypoglycaemia were the main reason in the other six patients	Complete withdrawal of hypoglycaemic medication over 3-6 months	NA	NA	NA	No deterioration of glycaemic control over the 1-year follow-up period. No significant difference between the mean HbA1c at the point of hypoglycaemic medications withdrawal and at 1 year of follow-up.	NR	NR
Hariya, 2014	Patients with HbA1c values ranging from 6.9-8.3% being treated with the highest approved doses of alpha-glucosidase inhibitors	Switching alpha-glucosidase inhibitors from acarbose or voglibose to miglitol and continued for 3 months	NA	NA	NA	Switch did not affect levels of HbA1c and fasting glucose. Glucose fluctuations were improved on switch.	No adverse events recorded	NR
Yoshida, 2016	Patients on haemodialysis and receiving subcutaneous insulin injection	Switching from subcutaneous injection of insulin to oral administration of a DPP-4 inhibitor. Oral vildagliptin at a low dose was started on the day insulin injection were discontinued	NA	NA	11 (55%) patients switched successfully	Glycated albumin was < 1.5% during the post switch	No adverse events recorded	NR
Andreassen, 2016	NA	Potential for deprescribing	NA	NA	Out of the total of 67 PIMs, the physician agreed that 26 of these could be discontinued without further question	NA	NR	NR
Hirakawa, 2016	Due to adverse effects, inability, or unwillingness to continue with medication	Permanent discontinuation of BP lowering medication. Based on a retrospective analysis of a database	Those who did not discontinue	1557 / 9583	14%	NR	Discontinuation of BP lowering medication was associated with HR (95% CI) of macrovascular events 3.23 (2.75-3.79); microvascular events 1.38 (1.11-1.71); and combined macrovascular and microvascular events 2.24 (1.96-2.57)	Discontinuation of BP lowering medication was associated with HR (95% CI) of mortality 7.99 (6.92-9.21);
Kondo, 2017	Patients on haemodialysis	Discontinuation of insulin and switching to liraglutide.	NA	NA	NA	Reduction in levels of HbA1c. Reduction in hypoglycaemic episodes	Significant decrease in cardiothoracic ratio on chest radiography. Improved quality of life in more than half of patients	NR

BP, blood pressure; CI, confidence interval; HbA1c, glycated haemoglobin; HR, hazard ratio; LDL-C, low density lipoprotein cholesterol; NA, not applicable; NR, not reported; PIM, potentially inappropriate medicine

SUPPLEMENTARY MATERIAL

Appendix 1	PRISMA checklist
Appendix 2	MOOSE checklist
Appendix 3	MEDLINE literature search strategy
Appendix 4	Modified Newcastle Ottawa Quality Scale for cross-sectional studies
Appendix 4	Methodological quality of eligible studies using the Newcastle Ottawa Quality Scale

Appendix 1. PRISMA checklist

Section/topic	Item No	Checklist item	Reported on page No
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable, background, objectives, data sources, study eligibility criteria, participants, interventions, study appraisal and synthesis methods, results, limitations, conclusions and implications of key findings, systematic review registration number	2
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	4
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (such as web address), and, if available, provide registration information including registration number	4
Eligibility criteria	6	Specify study characteristics (such as PICOS, length of follow-up) and report characteristics (such as years considered, language, publication status) used as criteria for eligibility, giving rationale	4
Information sources	7	Describe all information sources (such as databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Appendix 3
Study selection	9	State the process for selecting studies (that is, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	4-5
Data collection process	10	Describe method of data extraction from reports (such as piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	5
Data items	11	List and define all variables for which data were sought (such as PICOS, funding sources) and any assumptions and simplifications made	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	5, Appendix 5
Summary measures	13	State the principal summary measures (such as risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (such as I^2 statistic) for each meta-analysis	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (such as publication bias, selective reporting within studies)	5-6
Additional analyses	16	Describe methods of additional analyses (such as sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	NA
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	6 and Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (such as study size, PICOS, follow-up period) and provide the citations	7, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see item 12).	7, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present for each study (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot	7-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	7-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	7, Table 1; Appendix 5
Additional analysis	23	Give results of additional analyses, if done (such as sensitivity or subgroup analyses, meta-regression) (see item 16)	NA
Discussion			
Summary of evidence	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (such as health care providers, users, and policy makers)	10
Limitations	25	Discuss limitations at study and outcome level (such as risk of bias), and at review level (such as incomplete retrieval of identified research, reporting bias)	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	13
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (such as supply of data) and role of funders for the systematic review	13

Appendix 2. MOOSE checklist

Deintensification in older patients with type 2 diabetes: a systematic review of approaches, rates and outcomes

Criteria		Brief description of how the criteria were handled in the review
Reporting of background		
√	Problem definition	Recognising some harms of overtreatment, guideline bodies recommend de-intensification or deprescribing in older patients with diabetes. It is uncertain whether the benefits of deintensification outweighs the harms in these patients. We conducted a systematic review of published evidence, to assess deintensification approaches and rates and evaluate the harms and benefits of deintensification with antidiabetic medication and other therapies amongst older people (≥ 65 years) type 2 diabetes with or without cardiometabolic conditions.
√	Hypothesis statement	Circulating levels of OC are associated with cardiovascular outcomes
√	Description of study outcomes	Admission rates Hospitalisations Complications (e.g., hyperglycaemia, DKA, Hyperglycaemic Hyperosmolar Nonketotic Coma (HONK)) Falls Mortality Quality of life Patient satisfaction
√	Type of exposure	Deintensification approaches (stopping drug treatment entirely, reducing dose, gradual tapering, or substitution) of at least one medication
√	Type of study designs used	Observational (cross-sectional, prospective or retrospective case control, prospective cohort, retrospective cohort, case-cohort, or nested-case control) studies and clinical trials (randomised controlled trials including cluster and pragmatic trials and non-randomised controlled trials)
√	Study population	(i) included elderly patients (≥ 65 years) with type 2 diabetes and/or other cardiometabolic conditions (e.g., cardiovascular disease, hypertension) who were taking antidiabetic medication and plus other therapies for type 2 diabetes and other cardiometabolic conditions; (ii) reported deintensification approaches (stopping drug treatment entirely, reducing dose, gradual tapering, or substitution); and/or (iii) reported outcomes such as admission rates, hospitalisations, complications, quality of life, and patient satisfaction. The 65 years and older cutoff will apply if the average age of study participants age is 65 years or older; more than 75% of study participants are aged 65 years and older; or data from participants aged 65 years and older can be extracted from the study.
Reporting of search strategy should include		
√	Qualifications of searchers	Samuel Seidu, MD; Setor Kunutsor, PhD
√	Search strategy, including time period included in the synthesis and keywords	Time period: from inception of MEDLINE and EMBASE to 02 October 2018. **Search strategy:** The detailed search strategy can be found in Appendix 3.
√	Databases and registries searched	MEDLINE, Embase and Cochrane databases
√	Search software used, name and version, including special features	OvidSP was used to search Embase EndNote 9 used to manage references
√	Use of hand searching	We searched bibliographies of retrieved papers
√	List of citations located and those	Details of the literature search process are outlined in the flow chart.

	excluded, including justifications	The citation list for excluded studies is available upon request.
√	Method of addressing articles published in languages other than English	We placed no restrictions on language
√	Method of handling abstracts and unpublished studies	Not applicable
√	Description of any contact with authors	Not applicable
Reporting of methods should include		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria are described in the Methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, and outcomes
√	Assessment of confounding	Not applicable
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Study quality was assessed based on the nine-star Newcastle–Ottawa Scale using pre-defined criteria namely: population representativeness, comparability (adjustment of confounders), ascertainment of outcome and the Cochrane risk of bias tool
√	Assessment of heterogeneity	Limited data precluded assessment of heterogeneity
√	Description of statistical methods in sufficient detail to be replicated	Not applicable
√	Provision of appropriate tables and graphics	Table 1; Figure 1
Reporting of results should include		
√	Graph summarizing individual study estimates and overall estimate	NA
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	NA
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates
Reporting of discussion should include		
√	Quantitative assessment of bias	The systematic review is limited in scope, as it involves published data.
√	Justification for exclusion	All studies were excluded based on the pre-defined inclusion criteria in methods section.
√	Assessment of quality of included studies	Brief discussion included in 'Methods' section
Reporting of conclusions should include		
√	Consideration of alternative explanations for observed results	Findings should be interpreted with caution due to limited study and quality of study designs
√	Generalization of the conclusions	Discussed in the context of the results.
√	Guidelines for future research	We recommend definitive clinical trials
√	Disclosure of funding source	No separate funding was necessary for the undertaking of this systematic review.

Appendix 3. MEDLINE literature search strategy

1 exp Diabetes Mellitus, Type 2/ (120600)
2 exp Diabetes Mellitus/ (397262)
3 NIDDM.mp. (6891)
4 T2DM.mp. (16195)
5 exp Aged/ (2910982)
6 nursing home resident*.mp. (6065)
7 elderly.mp. (232319)
8 exp Aging/ (233498)
9 65 year.mp. (9083)
10 exp Geriatrics/ (29074)
11 older adult.mp. (6126)
12 older people.mp. (24923)
13 medication.mp. (218052)
14 exp Prescriptions/ (32535)
15 exp Hypoglycemic Agents/ad, ae, th [Administration & Dosage, Adverse Effects, Therapy] (37918)
16 antihyperglycemic.mp. (2511)
17 exp Metformin/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (8753)
18 exp Sulfonylurea Compounds/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (7667)
19 meglitinides.mp. (145)
20 exp Glyburide/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (2001)
21 exp Thiazolidinediones/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (5134)
22 glitazones.mp. (592)
23 exp Dipeptidyl-Peptidase IV Inhibitors/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (2576)
24 exp Glucagon-Like Peptides/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (2029)
25 exp Insulin/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (37615)
26 exp Insulin, Long-Acting/ or exp Insulin, Short-Acting/ (4659)
27 exp Antihypertensive Agents/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (110119)
28 exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (26195)
29 statin.mp. (20163)
30 exp Platelet Aggregation Inhibitors/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (57831)
31 Blood Platelet Antiaggregant*.mp. (0)
32 Platelet Inhibitor*.mp. (1325)
33 exp Cardiovascular Agents/ad, ae, tu [Administration & Dosage, Adverse Effects, Therapeutic Use] (399102)
34 cardiovascular drug.mp. (598)

35 deintensification.mp. (86)
36 de-intensify.mp. (12)
37 exp Deprescriptions/ (193)
38 withdraw*.mp. (123124)
39 ceas*.mp. (22534)
40 cessation.mp. (78878)
41 discontinu*.mp. (114282)
42 reduc*.mp. (3152639)
43 withheld.mp. (4417)
44 substitut*.mp. (346366)
45 stop*.mp. (122161)
46 eliminat*.mp. (300594)
47 taper*.mp. (18862)
48 1 or 2 or 3 or 4 (402270)
49 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (3137965)
50 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 (726827)
51 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (3991874)
52 48 and 49 and 50 and 51 (6997)
53 limit 52 to humans (6975)

****

Each part was specifically translated for searching alternative databases.

Appendix 4. Modified Newcastle Ottawa Quality Scale for cross-sectional studies

The methodological quality score is based on New-Castle Ottawa Quality Scale and is adapted for this review. Maximum of one star can be awarded for each item in Selection and Outcome categories. A maximum of two stars can be given for Comparability items.

Cut-off scores
Low methodological quality 0-3 stars
Moderate methodological quality 4-6 stars
High methodological quality 7-8 stars (>75%)

Category 1: Selection

1. Representativeness of the sample
(a) Truly representative if the sample is randomly derived from the general population with sample size of >100 subjects *
(b) Somewhat representative sample from the population with sample size of >100*
(c) Selected group of users (e.g., nurses, volunteers)
(d) No description of the derivation of the cases.

2. Non-respondents
(a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory*
(b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory
(c) No description of the response rate or the characteristics of the responders and the non-responders

3. Adequate definition of exposure
(a) Yes, according to a clear and widely used definition *
(b) Yes, from record linkage or based on self-reports
(c) No description.

4. Ascertainment of exposure
(a) Secure record*
(b) Written self-report
(c) No description

Category 2: Comparability

5. Comparability on the basis of the design/analysis
(a) Study controls for age, sex, or BMI*
(b) Study controls for any additional factor: Smoking status, education, alcohol intake, physical activity, lipids, or blood pressure)*

Category 3: Outcome

6. The study used a precise definition of outcome and valid and reliable method (individually for each relevant outcome)

7. Assessment of outcome
(a) Independent blind assessment (reference to medical records)*
(b) Record linkage (coded by ICD on database records)*
(c) Self-report.
(d) No description.

8. Statistical test

(a) The statistical test used to analyse the data is clearly described and appropriate, and the measurement of the association is present, including confidence intervals and the probability level (p-value)*
(b) The statistical test is not appropriate, not described or incomplete.

Appendix 5. Methodological quality of eligible studies using the Newcastle Ottawa Quality Scale

Author, year of publication	Selection (Max=4)	Comparability (Max=2)	Exposure (Max=3)	Overall Quality Score (Maximum=9)
Sjoblom, 2008	3	0	1	4
Lipska, 2010	3	2	3	8
Aspinall, 2011	3	2	2	7
Skoff, 2011	3	0	2	5
Hariya, 2014	2	0	1	3
Yoshida, 2016	2	0	1	3
Andreassen, 2016*	2	0	2	4
Hirakawa, 2016	3	2	3	8

*, this was based on Modified Newcastle Ottawa Quality Scale for cross-sectional studies as described in Appendix 4.