

MINI FOCUS ON DIABETES

JACC FOCUS SEMINAR: CV HEALTH PROMOTION

Blood Sugar Regulation for Cardiovascular Health Promotion and Disease Prevention



JACC Health Promotion Series

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ABSTRACT

The primary objective of this study was to analyze the most up-to-date evidence regarding whether and how blood sugar regulation influences cardiovascular health promotion and disease prevention by carrying out an umbrella review. Three separate, systematic literature searches identified 2,343 papers in total. Overall, 44 studies were included for data extraction and analysis. The included systematic reviews and meta-analyses published between January 1, 2016, and December 31, 2017, were of good to very good quality (median Overview Quality Assessment Questionnaire score = 17). Identified evidence suggests that cardiovascular disease (CVD) prevention services should consider regulation of blood glucose as a key target for intervention. Furthermore, the recommendations for effective intervention and service development/training described here for prevention of CVD should be adopted into evidence-based practice guidelines. Multidisciplinary teams should be formed to deliver multicomponent interventions in community-based settings. There may be substantial opportunities for integrating CVD and diabetes prevention services.

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The prevalence of cardiovascular diseases (CVDs) is increasing worldwide (1). The absolute number of deaths caused by CVD increased by more than 25% between 1990 and 2010 (2), while decreasing in higher-income countries (3). As the number of patients with CVD is likely to increase further due to demographic changes, so will the costs of treatment (4). Hyperglycemia is a

key modifiable risk factor for the development of CVD (5-8), with pre-diabetes being a major risk factor for the progression to type 2 diabetes mellitus (T2DM), which, in turn, increases CVD risk (9). As a part of a multifactorial risk factor intervention, effective reduction of hyperglycemia has a positive effect on CVD risk (10). This is true for both high and low levels of glycosylated hemoglobin (HbA_{1c})



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ABBREVIATIONS AND ACRONYMS

BP	= blood pressure
CI	= confidence interval
CV	= cardiovascular
CVD	= cardiovascular disease
DBP	= diastolic blood pressure
DM	= diabetes mellitus
DPP	= dipeptidyl peptidase
GLP	= glucagon-like peptide
GLP-1 RA	= glucagon-like peptide-1 receptor agonist
HbA_{1c}	= glycosylated hemoglobin
IQR	= interquartile range
MI	= myocardial infarction
OQAQ	= Overview Quality Assessment Questionnaire
RCT	= randomized controlled trial
SBP	= systolic blood pressure
SGLT2	= sodium-glucose cotransporter 2
T2DM	= type 2 diabetes mellitus

at baseline (11-13). For reasons not well understood so far, only nonfatal events could be reduced by intensive glucose lowering (14,15). Therefore, it is vital to understand the potential prevention and care pathways by which CVD risk is reduced by blood sugar regulation to guide prevention of CVD.

Established mechanisms in cardiovascular (CV) health promotion entail developing strategies for screening and preventive interventions tackling the mechanisms of disease development (16). Although trials of intensive glucose reduction via medication in the past decades showed no significant macrovascular benefits (17), recent studies of glucose lowering using glucagon-like peptide (GLP)-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors have shown sizable reductions in hard CVD endpoints compared with established glucose-lowering strategies (18,19). This highlights the importance of the mechanisms tackled by these drugs in preventing CVD in patients with diabetes mellitus (DM). At the same time, lifestyle interventions focusing on improving diet, weight loss, and physical activity are known

to be highly effective in preventing progression to T2DM in persons with hyperglycemia and increased risk of DM and CVD (20,21). Risk factors for CVD overlap, because high blood pressure (BP), weight, physical activity, cholesterol, diet, and blood sugar are all interconnected. However, progression to T2DM adds considerable risk due to the micro- and macrovascular complications of endocrine dysregulation (22). Indeed, nearly 5 decades of research in DM prevention and management have largely focused on interventions to identify risk, address behavioral risk factors, and improve management of blood sugars, BP, and lipids. There is, therefore, an opportunity for preventing CVD risk by focusing on the identification of mechanisms leading to CVD in people with hyperglycemia and taking steps to regulate blood glucose.

However, considerable debate remains in the medical and public health communities about whether individual-focused screen-and-treat interventions are: 1) sufficient; and 2) the most cost-effective approaches (23-26). The benefit from individual-focused interventions is potentially lifesaving for individuals with high risk or established disease but reaches only a small fraction of the population (27). Because T2DM and downstream CVD are both associated with wider cultural and societal influences (28), there have

been several calls for broader, more population-focused interventions that can reach larger groups of people. Some have suggested that policy interventions that use regulations, mass media or educational approaches, or environmental changes (29-33) will have broader, more cost-effective, and sustainable impacts on DM and CVD. A whole-population approach aims to minimize the entire distribution of a risk factor, even if just by a small degree, to affect the proportion of those at risk (34).

Evidence-based guidance on individual- or population-based, as well as standardized care and prevention pathways are needed to integrate current evidence from trials into guidelines, practice, and policies (35).

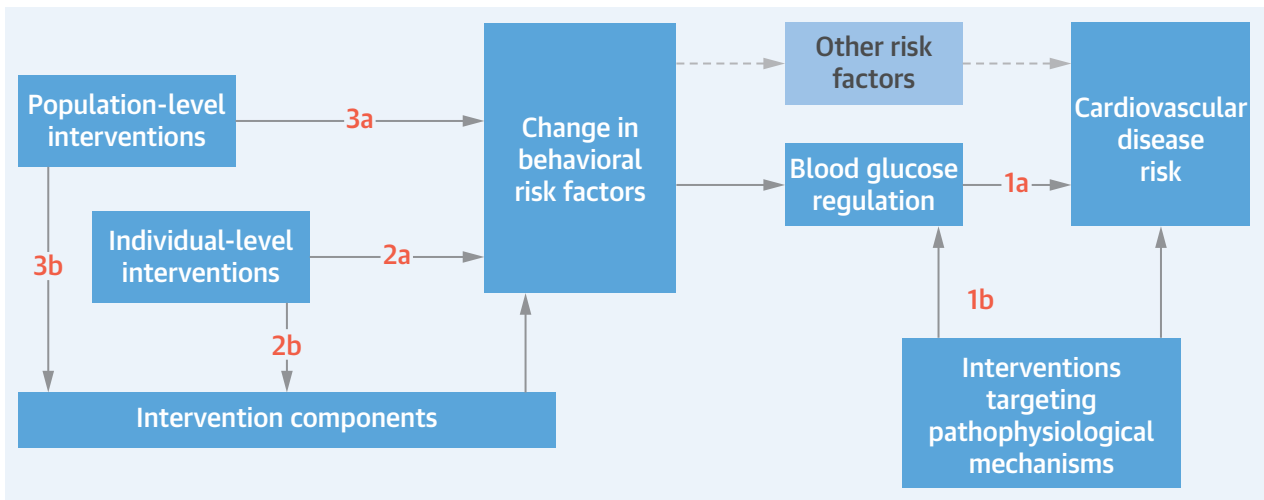
OBJECTIVES

The main objective of this study was to carry out an umbrella review (36) of recent evidence on interventions—both medical treatments and lifestyle modification—targeting blood sugar regulation. This will help to inform efforts to improve CV health via a more detailed consideration of blood glucose regulation pathways. Based on Andersen's Model of Health Services' Use (37), the study group combined 4 perspectives in 1 overall review. The structure of the review covers medical treatments of blood sugar regulation contributing to CVD risk, factors influencing individual health behavior, and factors enabling population-based interventions. Based on this model, guidance for the development of future health promotion programs and competencies for training can be derived.

As shown in the **Central Illustration**, the specific objectives are:

- To outline likely pathophysiological mechanisms by which blood glucose regulation affects CVD risk and evidence on pharmacological interventions targeting these pathways (**Central Illustration 1a and 1b**);
- To identify evidence-based individual-level interventions for supporting effective behavior change to regulate blood sugar and thereby reduce CVD risk (**Central Illustration 1a and 1b**);
- To identify evidence-based population-level interventions for supporting effective behavior change to regulate blood sugar and thereby reduce CVD risk (**Central Illustration 2a and 2b**);
- To translate key findings into applicable recommendations highlighting competencies for training for health promotion and for standardizing health promotion care pathways (**Central Illustration 3a and 3b**).

CENTRAL ILLUSTRATION Blood Sugar Regulation: Logic Order and Interdependencies



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Cardiovascular disease (CVD) risk is influenced by blood glucose regulation, and both CVD risk and blood glucose regulation are influenced by interventions targeting pathophysiological mechanisms (1a, 1b). Other risk factors also affect CVD risk. Blood glucose regulation and other risk factors are, in turn, influenced by changes in behavioral risk factors. Population-level (3a, 3b) and individual-level (2a, 2b) interventions and intervention components influence the behavioral risk factors, influencing blood glucose regulation and, ultimately, CVD risk. Boxes represent the objectives of the individual review sections; arrows show the interdependencies of the objectives for their contribution to the explanation of CVD risk.

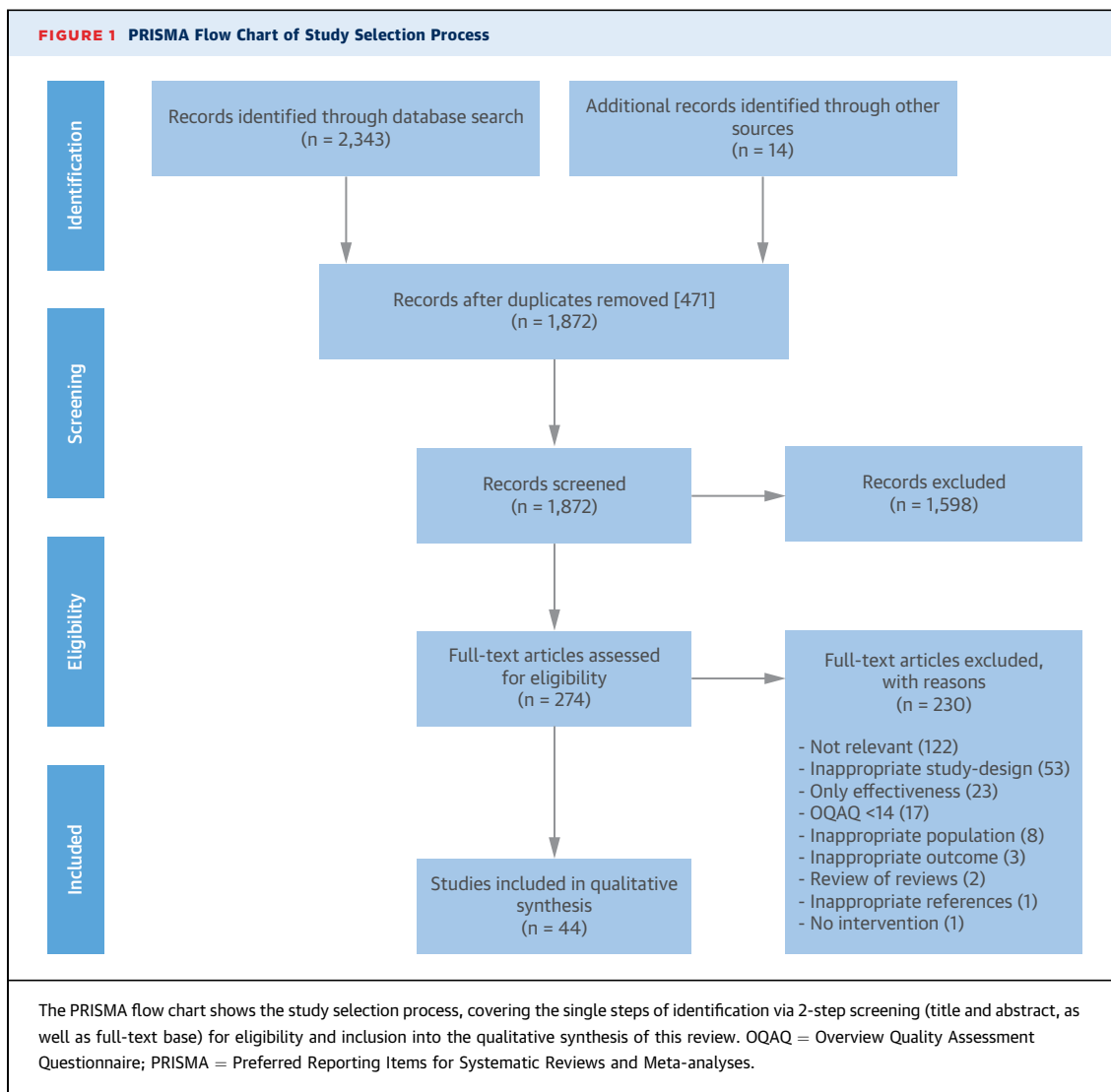
METHODS

In order to address these objectives, extensive automated and manual searches were performed to identify relevant systematic reviews of randomized controlled trials (RCTs) and meta-analyses. Database reviews were conducted, duplicate reviews were removed, and search results were triaged to the section writing teams. The 3 core sections aimed to answer the primary research question: In what ways should blood sugar regulation be taken into account by future CV health promotion and prevention programs? Two reviewers per section completed screening of studies, data extraction, and quality assessments. Any discrepancies between the reviewers were resolved by discussion.

SEARCH STRATEGY AND ELIGIBILITY CRITERIA.

Comprehensive electronic searches were conducted in Medline and Embase for systematic reviews of RCTs or meta-analyses published between January 1, 2016, and December 31, 2017. The search areas were MeSH terms or title, abstract, and key words. To identify the main physiopathological mechanisms driving CV outcomes in patients with T2DM (Section 1), the search terms and synonyms covered the following criteria: study designs (systematic reviews and

meta-analysis of RCTs); interventions (glucose lowering, in combination with BP and lipid lowering); mechanisms (physiopathological, pathophysiological); and measured outcomes (BP regulation, lipid profile regulation, CV events, and mortality). To identify intervention components associated with the effectiveness of individual-level behavior change to address blood glucose regulation (Section 2), search terms were identified and searches were constructed to combine each of the following areas: CVD risk factors; blood sugar regulation; behavioral intervention targets; and specific study designs (systematic reviews and meta-analysis of RCTs). To investigate population-level interventions (Section 3), a search for reviews of exposures such as mandates, policies, programs, mass education, or built environmental changes that may be associated with widespread changes in blood sugar was conducted. Systematic reviews and meta-analyses reporting glucose-related outcomes, both actual blood glucoses (HbA_{1c}, fasting blood glucose) or diabetes-related outcomes (prevalence, incidence, or rates of acute or chronic complications) were included. Papers identified in any of the previous searches focusing on standardized care pathways, especially interventions in the primary care setting, were summarized in Section 4.



We hand-searched any systematic reviews and meta-analyses to include studies that may have been missed by the automated search. In order to provide a consistent picture of the current state of the art, single landmark studies from the past 15 years were included, as well as highlights of expected findings derived from current studies.

After screening of title and abstracts, all sections excluded reviews or meta-analyses that did not include humans, did not meet 1 of the 4 aims, or were published before January 1, 2016. Although originally intended, a thorough focus on systematic reviews and meta-analyses primarily derived from RCTs was not feasible for population-level interventions (section 3) because their characteristics hardly allow for testing in an experimental setting. After full-text screening, studies were excluded if they did not inform the

research question or were below the threshold of the Overview Quality Assessment Questionnaire (OQAQ) measurement (see the next section).

QUALITY ASSESSMENT AND STANDARDIZED REPORTING. For quality assessment of the identified reviews, a modified version of Oxman and Guyatt's OQAQ (38) was used. The OQAQ consists of 9 quality items, each comprising the dimensions "yes," "no," or "partially/can't tell," carrying scores of 2, 1, and 0, respectively, resulting in an overall score of 0 to 18 points. To maximize the quality of evidence considered, we rejected studies with an OQAQ score <14.

Standardized reporting was ensured by applying the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting framework (39).

DATA EXTRACTION AND ANALYSIS. Although carried out independently, the 3 sections applied identical

methods for data extraction, analysis, and reporting. A revised template for extracting/summarizing empirical evidence from a prior systematic review of reviews (40) was applied. Not all included systematic reviews and meta-analyses referred to glycemic control as a primary outcome or distinguished between primary, secondary, and surrogate outcomes. Therefore, a presentation of results according to the outcome levels is not provided. Finally, implications for standardizing health promotion care pathways and competencies for health care workers were extracted from each of the 3 sections.

RESULTS

SECTION 1: PATHOPHYSIOLOGICAL PATHWAYS OF BLOOD GLUCOSE REGULATION ON CVD RISK.

Review characteristics. Overall, 769 references were identified, including 455 from our section-specific search string, 305 from the searches for Sections 2 and 3, and 9 from hand-searching (Figure 1). After reviewing the titles and abstracts, 685 studies were excluded. Details of the evidence extracted are provided in Online Table 1.

Study quality. On a scale of 0 to 18, the median OQAQ score of 17 included studies was 17 (interquartile range [IQR]: 15 to 18), indicating that they were high-quality systematic reviews and meta-analyses.

Outcomes and mechanisms. Individuals with T2DM have a 2- to 3-fold greater risk of CVD than people without T2DM, with women showing an increased elevated risk compared with men (2.5-fold risk increase in women vs. 1.7-fold in men) (41). Moreover, people with T2DM have an increased risk of long-term mortality following coronary revascularization in both stable ischemic and acute coronary syndrome populations (42-46). Through outlining the recently analyzed glucose-lowering pharmacological interventions, the pathophysiological mechanisms leading to CV events in T2DM patients are presented.

Intensive glucose lowering in landmark trials such as the UKPDS (United Kingdom Prospective Diabetes Study) (47), ACCORD (Action to Control Cardiovascular Risk in Diabetes; NCT0000620) (17), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) (27), and VADT (Glycemic Control and Complications in Diabetes Mellitus Type 2; NCT00032487) (48) trials, mainly using insulin or sulfonylureas, had improved microvascular, but not macrovascular outcomes, suggesting that glucose lowering in itself does not reduce CV events. Hence, reduction of hyperglycemia using insulin therapy does not reduce the risk of CV

events (49). Metformin may lower the incidence of CVD, but this is still not proven (50). Moreover, the latest analyses addressing intensive glucose lowering show that in comparison to less-intensive therapy, intensive glucose lowering had no influence on CV mortality, but reduced the risk of myocardial infarction (MI) (51), in addition to a reduction in the risk of diabetic nephropathy and retinopathy (52). Hence, managing blood glucose alone in T2DM does not seem to reduce macrovascular CV events and targeting other mechanisms should be explored.

Using dipeptidylpeptidase (DPP)-4 inhibitors for glycemic control through augmenting the bioavailability of GLP-1 held the promise of improved CV outcomes from preclinical studies, but it has failed to be proven in clinical trials to date (53). Some DPP-4 inhibitors even increase the risk of hospitalization for heart failure (54). Given the broad physiological activity and distribution of DPP-4, speculation arose about the off-target effects of DPP-4 inhibitors, including their impact on the sympathetic nervous system leading to cardiotoxicity (55). Although GLP-1 RAs reduce hyperglycemia through the same pathway as DPP-4 inhibitors, they are associated with improved CV outcomes and have fewer adverse effects.

Meta-analyses found that GLP-1 RAs: 1) reduced body weight, systolic blood pressure (SBP), triglycerides, and low-density lipoprotein cholesterol better than insulin (56); 2) were associated with a lower risk of MI after long-term treatment in comparison to sulfonylurea-based therapy (18); 3) reduced the risk of all-cause and CV mortality in comparison to placebo (57,58); 4) reduced the risk of severe hypoglycemia (57); and 5) did not increase the risk of heart failure, stroke, and microvascular complications, including diabetic retinopathy and nephropathy (58). However, 1 GLP-1 RA, exenatide, was found to increase the risk of arrhythmias in patients with T2DM (54). The mechanisms through which GLP-1 RAs reduce CV risk beyond glucose-lowering effects possibly include reduction in body weight, lipids, BP, inflammatory markers, oxidative stress, endothelial dysfunction, and subclinical atherosclerosis (59).

Similar to GLP-1 RAs, SGLT2 inhibition reduces SPB and diastolic blood pressure (DBP) (60-62) besides reducing glucose reabsorption in the kidney, inducing glucosuria and thereby reducing blood glucose. Moreover, SGLT2 inhibition reduces all-cause and CV mortality and major CV events (19,53,62,63). Controversies arose, however, regarding the risk of stroke, which ranged from no effect (53,62,63) to increased risk (19). The most prominent explanation for cardioprotection is the diuretic effect of empagliflozin

and the consequent reduction in plasma volume (64). Although conventional diuretic agents and thiazides show moderate or no reduction in risk of heart failure, the diuretic action of empagliflozin does not induce reflex activation of the sympathetic nervous system and the consequent neurohormonal cardiac dysregulation. Moreover, the proximal inhibition of glucose and sodium reabsorption has beneficial consequences on renal function, as opposed to distal inhibition (65). Other cardioprotective mechanisms include regulation of metabolic processes, such as increased plasma glucagon (66) and ketone (67) concentrations, and reduced uric acid serum levels conferring protection against increased BP and vascular damage (68). Another theory is derived from data on reduced vascular oxidative stress and inflammation after treatment (69), conferring a reduction in aortic stiffness, an independent risk factor for CV mortality (70). Hence, the metabolic effects of SGLT2 inhibitors leading to weight loss, BP reduction, natriuresis, and improved renal function reduce major adverse cardiac events, primarily CV death, independent of its glucose-lowering activity. Whether use of these agents alone eliminates the need for BP- and lipid-lowering therapies needs to be addressed.

The landmark trials (17,27,47,48) investigated combining intensive glucose lowering with BP- and lipid-lowering therapies, termed multifactorial interventions. In recent analyses, multifactorial interventions reduced CV mortality in addition to improving CV outcomes (71). However, intensive BP lowering in (already well-controlled) patients with T2DM had more risks than benefits. In one analysis, the renin-angiotensin system blockers were most effective in patients with T2DM in reducing CV risk versus placebo, but there was little or no further benefit in lowering SBP below 130 mm Hg (72). Furthermore, although antihypertensive treatment reduced the risk of all-cause mortality, MI, and heart failure in patients with T2DM and baseline SBP between 140 and 150 mm Hg, the risk of CV mortality increased if the baseline SBP was lower than 140 mm Hg (73).

Taken together, the analyses presented in the preceding text suggest that pharmacological interventions improving glycemic control in people with T2DM can lead to improvements in CV outcomes. BP regulation seems to be a key pathway mediating this effect. Preventing progression to T2DM in those at risk is also a key risk-reduction pathway.

Strengths and limitations. The included reviews are of high quality and represent the latest evidence

of intervention efficacy in relation to CVD risk reduction through blood glucose management in adults with T2DM. Although many studies of a case-control or an observational nature addressed the association of genetic polymorphisms with increased risk of CV outcomes in people with T2DM, the exclusion of non-RCT studies from our review minimized the comprehensiveness of mechanisms and interventions reviewed.

SECTION 2: INDIVIDUAL-LEVEL INTERVENTIONS FOR SUPPORTING BEHAVIOR CHANGE TO REGULATE BLOOD SUGAR. Evidence from landmark studies. Three “landmark” papers were identified in relation to making recommendations on the optimal content of individual lifestyle interventions. These were a prior systematic review of reviews of diet and physical activity interventions (40), U.S. national standards for diabetes self-management education and support (74), and public health guidance on diabetes prevention from the United Kingdom’s National Institute for Health and Clinical Excellence (75). Existing recommendations from these sources are summarized in **Table 1** and are supplemented with the main evidence from the current review.

Review characteristics. Intervention characteristics. Our searches identified 861 papers, of which 24 met both the selection and quality criteria (26,76–98) (**Figure 1**). The characteristics of the included reviews are provided in **Online Table 2.1**. We identified 95 analyses relating intervention components to effectiveness (**Online Tables 2.2 to 2.9**) and 19 effectiveness analyses (**Online Table 2.1**). Full details of these 114 analyses are presented in **Online Table 2.2**.

Study quality. The methodological quality of included reviews was generally good (median OQAQ score = 16; IQR: 14 to 18). The most common methodological weakness was the lack of use of study quality data to inform analyses (e.g., by excluding low-quality trials).

Outcomes/effective components of interventions.

Overall effectiveness. Evidence from 7 systematic reviews (26,79,86,91,94,95,98) found that individual lifestyle interventions targeting physical activity and/or diet were effective in reducing blood glucose (HbA_{1c}, fasting plasma glucose, fasting insulin, Homeostatic Model Assessment for Insulin Resistance, and 2-h blood glucose) for up to 54 months, reducing diabetes incidence in people at risk of developing T2DM for up to 72 months, and in reducing weight at up to 52 months of follow-up. However, there was considerable variation in outcomes between studies, indicating the importance of understanding what content and delivery factors are associated with increased effectiveness.

TABLE 1 Evidence-Based Recommendations on Content for Interventions to Manage Blood Glucose and CV Risk Via Changes in Diet and PA

Existing Recommendation (From Prior Landmark Studies/Guidelines)	New Evidence/Updates
To maximize weight loss, interventions should promote changes in both diet and PA (40,75).	Evidence from the current review supports the extension of this recommendation to maximizing blood glucose reduction (85,89). The addition of physical activity to diet may have less effect on FPG or HOMA-IR (98), however.
Interventions should use established, well-defined BCTs (e.g., motivational interviewing, action planning, relapse prevention) (40,75). Note: Such intervention strategies are defined in recent taxonomies of BCTs (145).	Evidence from the current review supports the extension of this recommendation as follows: The use of behavior change theory in designing interventions may help to increase effectiveness for reducing HbA _{1c} (86,92). However, further evidence is needed on which specific theoretical elements are essential/optimal. Providing people with meals to ensure a balanced diet is effective for reducing HbA _{1c} for up to 24 months (86). This strategy may be particularly suited for people with low problem-solving capabilities. More research is needed on cost-effectiveness and sustainability. Recent evidence on motivational interviewing for blood glucose reduction is mixed, and this may reflect a need for high-quality delivery/provider skills to ensure success (77,81). Including problem-solving and social comparison techniques were associated with increased effectiveness (86), as was the use of self-regulation techniques (see following row).
Interventions should encourage the use of “self-regulation” techniques, which are associated with increased effectiveness. Self-regulation includes: specific and individualized goal setting; prompting self-monitoring; providing feedback on performance, and review of behavioral goals (40,75).	Evidence from the current review supports the extension of this recommendation: As well as self-monitoring of weight or PA, self-monitoring of blood glucose may be useful for some people with T2DM to help regulate blood glucose (82). Due regard is needed to ensure “meaningful monitoring” and avoid possible anxiety or frustration in individual cases.
Intervention content and delivery should be tailored to individual needs, culture, and capabilities (e.g., problem-solving skills, literacy) (74,75).	The current review identified no new evidence on this issue.
Interventions should encourage participants to engage social support for behavior changes (i.e., engage others who are important, such as family, friends, and colleagues) (40,75).	The current review identified no new evidence on this issue. However, evidence on the benefits of problem-solving (previous row) and expert opinion suggests that it may be important to address negative social influences as well as to engage positive social support.
Interventions may be delivered by a wide range of people/professions, subject to appropriate training. This may include doctors, nurses, dietitians/nutritionists, exercise specialists, and lay people, often working within a multidisciplinary team (40). At least 1 of the team members responsible for facilitating diabetes self-management services should be a suitably trained registered nurse, registered dietitian/nutritionist, pharmacist, or certified diabetes educator (74).	Evidence from the current review was broadly consistent with the existing recommendation and also provided examples of effective glucose-reduction in interventions led by health professionals working alongside peer supporters and pharmacists (88,92,93). Including a dietitian in the provider team is specifically recommended for increasing effects on glucose and weight in interventions with a dietary component (86,90,95). Interventions led by peers were less effective for reducing blood sugar than those led by health professionals (92).
Interventions may be delivered in a wide range of settings, including health care settings, the workplace, the home, and in the community.	The current update did not identify evidence on this issue.
Interventions may be delivered using group, individual, or mixed modes (individual and group).	Evidence from the current review is consistent with this recommendation.
Interventions should include a strong focus on maintenance. It is not clear how best to achieve behavior maintenance, but techniques designed to address maintenance include: self-monitoring of progress; providing feedback; reviewing of goals; engaging social support; use of relapse management techniques; and providing follow-up prompts.	The findings of this review were consistent with this recommendation (see section on overall effectiveness).
Interventions should maximize the frequency or number of contacts with participants (40,75). The intensity of intervention should be matched to the level of risk for progression to/of T2DM (75).	Evidence from the current review is consistent with the existing recommendations. For instance, interventions lasting 36-72 months reduced diabetes incidence and the number needed to treat more than interventions lasting 6-24 months (26).
Intervention programs should adopt a person-centered, empathy-building approach (74,75).	Evidence from the current review is consistent with this, although a need for high-quality delivery was identified (see earlier evidence on motivational interviewing).
Offer follow-up sessions/support/reviews of progress at regular intervals following the initial intervention period to reinforce positive behavior change and provide support in case of relapse (74,75).	Evidence from the current review was consistent with this recommendation. For example, contacting participants for the remainder of the follow-up period to promote continued adherence to healthy lifestyle principles was associated with increased maintenance of effects on weight and FPG (75).
Incorporating text messaging into diabetes self-management interventions improves engagement and outcomes. Along with other digital health technologies, it may be possible to establish a self-management feedback loop with 4 key elements to provide ongoing, real-time engagement in self-management (74): 1. Two-way communication; 2. Analysis of patient-generated health data; 3. Customized education; 4. Individualized feedback.	The current review supports and extends this recommendation. Web-based interventions, text messaging, and mobile phone apps all had significant effects in reducing HbA _{1c} at 3-12 months of follow-up (80,83,85,87,96,97). Digital interventions were also effective for increasing PA (85,87) and reducing weight (78,85,87,96) in the short term (8-12 months). Further evidence, although mixed, suggests that the addition of in-person support increases effectiveness for weight loss (78,85,91). Hence, the use of “blended” interventions (where patients collect and share data on target behaviors/health outcomes with intervention providers/health professionals to facilitate a tailored discussion) is recommended to support lifestyle behavior change.

The left column indicates existing recommendations based on prior landmark studies and guidelines); the right column shows what the current review adds.
 BCT = behavioral change technique; CV = cardiovascular; FPG = fasting plasma glucose; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; HbA_{1c} = glycosylated hemoglobin; PA = physical activity; T2DM = type 2 diabetes mellitus.

Evidence from 6 systematic reviews focusing on maintenance of effects (26,76,85,86,91,98) found a reduction in effects on both blood glucose and weight over time (for up to 60 months of follow-up).

Components of interventions associated with increased effectiveness. Recommendations derived from both the current review and the landmark papers are presented in [Table 1](#).

Strengths and limitations. The included reviews are of high quality and represent the latest evidence on components of interventions related to effectiveness in reducing blood sugar and the related risk factors of weight and physical activity. Our consideration of evidence relating to blood glucose regulation adds meaningful new recommendations to existing guidance on CV risk prevention ([Table 1](#)). Relating the findings to prior evidence-based recommendations helps to minimize sampling bias due to the time limits on our search strategy. However, as most interventions targeted multiple behaviors, it was impossible to identify components associated with changes in specific behaviors.

SECTION 3: POPULATION-LEVEL INTERVENTIONS FOR SUPPORTING BEHAVIOR CHANGE TO REGULATE BLOOD SUGAR. Review characteristics. Based on the electronic database searches, 85 papers were assessed for inclusion. Of these, 75 were excluded because the systematic review objectives were unrelated (34), or the reviews evaluated individual-focused interventions (17) and/or assessed clinical care models (10) or competencies of personnel (14) to address diabetes prevention or management. Although an additional hand search was carried out, no additional systematic reviews that met the eligibility criteria were identified. Characteristics of the included studies can be seen in [Online Table 3](#).

In total, 10 full-text papers were reviewed for inclusion. Of these, 7 review papers were excluded for the following reasons: did not report glucose-related outcomes ($n = 3$); were not reviews of population-level interventions ($n = 2$); or only included 1 study with both a population-level intervention and a glucose outcome ($n = 2$). The 3 remaining papers included 1 systematic review (99) and 2 systematic reviews/meta-analyses (100,101).

Study quality. All included studies were of excellent quality, scoring 17 or higher on an 18-point scale.

Outcomes/effective components of interventions. Each of the included studies did not focus on unique intervention strategies; instead, they summarized the results related to population-level efforts targeted at a particular disease-related outcome (recognizing early symptoms for type 1 diabetes (99) or a specific community setting (worksites [100,101]). Deylami

et al. 99) summarized the evidence for awareness campaigns about early type 1 diabetes symptoms in children targeted to the population and primary health care professionals. The investigators reported that the programs, which included educational posters, reusable shopping bags, and/or provision of glucose-testing equipment to health care providers, reduced the rates of diabetic ketoacidosis (rates of diabetic ketoacidosis were reduced in 4 of 7 studies).

Two reviews (100,101) summarized the data around worksite-based changes and cardiometabolic outcomes. Both reviews included studies using a variety of intervention models including 1 or more of the following: individual or group-based education; medical testing; electronic messaging; online programs; self-monitoring of weight and/or physical activity; physical activity prescriptions; educational materials; active workstations; and provision of healthy meals. Reed et al. (100) reported on 24 studies (20 were included in the meta-analysis) that examined the effectiveness of workplace interventions for improving moderate-to-vigorous activity levels and cardiometabolic outcomes among working adult women in high-income country settings. Two of the included studies reported changes in blood glucose; in the meta-analysis, these interventions were shown to significantly reduce blood glucose levels among participants (-0.18 mmol/l; 95% confidence interval [CI]: -0.29 to -0.07). In their meta-analysis, Shrestha et al. (101) concluded that workplace dietary interventions significantly reduced HbA_{1c} and fasting glucose among participants (pooled results from the meta-analysis: 0.18% reduction in HbA_{1c}; 95% CI: -0.29 to -0.06 ; -2.60 mg/dl fasting glucose; 95% CI: -5.27 to 0.08).

Two of the excluded papers included very limited data (1 study in each review) around population-based interventions and glycemic outcomes. In their review of interventions to reduce ischemic heart disease in sub-Saharan Africa, Ebireri et al. (102) included 1 study that showed a mass-media education campaign had no effect on fasting blood glucose levels (103). When reviewing the associations between medication copays and both medication adherence and health outcomes, Gourzoulidis et al. (104) found only 1 study that reported HbA_{1c} outcomes after a copay increase (a \$5 copay increase was significantly associated with a 0.1-point increase in HbA_{1c} [105]).

Large-scale dissemination and implementation research related to health policies for diabetes is still nascent. Although RCTs and, especially, meta-analysis of RCTs are considered the strongest research designs to infer causation (106), many environmental-level, system-level, employer-level, or

even government-level policy interventions are often not amenable ethically or physically possible to evaluate using RCTs. However, causal inference can be enhanced through the use of rigorous quasiexperimental study designs and sophisticated analytical techniques (107,108). Furthermore, many environmental changes (109), as well as regulatory, payment, employer, and health system policies and programs may be opportunities for natural experiment evaluations; here, the investigator does not control the intervention but uses the opportunity and easily available data sources to assess whether these policies and programs had the intended effects (110), as well as any unintended societal consequences. Many of the studies assessing the influence of policies on detection, prevention, and management of diabetes have tended to use quasi-experimental designs (111,112).

Many existing studies, as well as those included in this review, only include intermediate outcomes and not hard health outcomes; for example, a review of food policies seeking to reduce adult obesity and diabetes in the United States reported that most studies focused on food purchasing patterns (54% of included studies) or self-reported food consumption (46%), with only 34% including body weight/composition as outcomes (113). Furthermore, studies with biomedical outcomes were more likely to be of lower quality and less likely to show positive results (114).

Strengths and limitations. There are limited data on the effectiveness of population-based interventions for improving glucose outcomes, including both blood glucose levels (HbA_{1c}, fasting blood glucose) or diabetes-related outcomes (prevalence, incidence, or rates of acute or chronic complications). No evidence was found solely for T2DM. Among the studies identified for this review, only 3 systematic reviews included sufficient data on glycemic outcomes to be included. Furthermore, much of the existing evidence for population-based interventions relies on observational studies and should be interpreted with caution.

SECTION 4: COMPETENCIES AND HEALTH PROMOTION CARE PATHWAYS: ANALYSIS OF STUDIES RELATING TO COMPETENCIES AND STANDARDIZED HEALTH PROMOTION CARE PATHWAYS. Review characteristics. Across the 3 searches, 12 systematic reviews and meta-analyses were identified as relating to health care worker involvement and task shifting toward health practitioners other than doctors, whereas 3 other studies focused on integrated care (e.g., applying care models or evaluating quality improvement). Characteristics of the included studies can be seen in [Online Table 4](#).

Integrated care is defined following Godwin's health-system-based definition, as a "continuum of health promotion, disease prevention, diagnosis, treatment, disease-management, rehabilitation and palliative care services, coordinated across the different levels [...] of care" (114).

Study quality. The methodological quality of included reviews was generally good (median OQAQ score = 16; IQR: 14 to 18). The main methodological weaknesses were a lack of quality assessment and sensitivity analyses. Additional issues were not reporting the number of included patients in analyses, missing power analysis, and poor reporting on handling of dropouts/missing data/use of intention-to-treat analysis.

Outcomes/effective components of interventions. The 3 studies focusing on integrated care using standardized approaches such as the chronic care model were all concerned with the management of T2DM (115-117). However, there is a lack of good-quality evidence on CV risk factor improvement via integrated care (118). Although the chronic care model used in primary care was evaluated as highly effective in reducing mortality and HbA_{1c}, standardized European approaches in multifaceted diabetes care showed only small improvements in clinical outcomes such as HbA_{1c}. However, 1 review reported a higher potential for newly diagnosed patients (116). With respect to integrated care in general, improvement was shown, not only in patient outcomes, but also for process costs and health service utilization rates (117).

Pharmacist interventions to reduce the burden of CVD and T2DM were especially effective when pharmacists performed a clinical decision-making process as part of a multidisciplinary health care team (93). Although improvements in clinical outcomes such as HbA_{1c}, DBP/SBP, or cholesterol were only short-term (118), the effect size compared well with care delivered by primary physicians (93,118,119) and was found in various settings, including primary care and hospitals (93).

Community-based approaches vary in the type of health care professional involved. The majority of the reviews (120-124) were concerned with the involvement of community-based pharmacists in the management of CVD or T2DM; 2 focused on community health worker involvement (121,125), whereas 1 involved community-based nurses (126). Regardless of the health practitioners involved, 6 studies reported improvements in clinical outcomes, such as HbA_{1c}, DBP/SBP, glycemic as well as lipid control, and all-cause mortality (120-123,125,126). Three studies showed improvements in medication

adherence (122-124). For health-related outcomes of interventions delivered by community-based pharmacists, such as quality of life, adherence to treatment and/or medication, and achievement of health goals, the results are more heterogeneous. Their effectiveness relies highly on patient-centeredness (i.e., whether they take into account their patients' health beliefs, goals, and literacy) (122). Interventions by community-based health workers were reported to be as effective in achieving lifestyle change in obese patients as similar interventions in other primary care settings (121,125). They were, however, inferior to commercial weight-loss programs for generating weight loss (124). Mixed, yet overall positive, results were found for the effect of community-based pharmacists on health resource usage, including hospitalization rates and urgent care and emergency department visits (123). However, there is low-strength evidence of the effectiveness of chronic disease management supervised by pharmacists when studying clinical outcomes such as clinical CV events and all-cause mortality (123).

Two reviews reported pharmacist-led interventions to be cost-effective (123,124). It is worth noting that the positive effect of team approaches or at least strong connections between physicians and community-based health practitioners were reported as key factors in the success of such interventions (121,122).

One review found equally good glycemic outcomes for nurses prescribing glucose regulation medication compared with physicians (127), but not when compared with multidisciplinary teams. However, the lack of evidence for CV care, indicated by a low number of studies reporting adverse events (125) as well as missing long-term clinical outcomes (121), calls for more research on evidence-based health promotion care pathways.

Strengths and limitations. No individual search string was applied to identify relevant published studies for this part of the review. Included studies were identified as a part of the search process identifying published studies for individual- and population-level interventions.

Implications derived from Sections 1, 2, 3, and 4. Recommendations for service design/delivery and the training of health care professionals involved in CVD prevention, drawn from the evidence in all 4 sections, are summarized in Table 2.

DISCUSSION

This umbrella review summarizes recent high-quality systematic reviews and meta-analyses, including

evidence on pathophysiological, individual-level and population-level interventions to regulate blood glucose in people at risk of CVD. These findings may serve to help stakeholders develop recommendations for blood sugar regulation to reduce CV risk (Table 2).

An overview of the efficacy of interventions on the individual or population levels to regulate blood sugar is presented, with an emphasis on the need to reduce CV risk.

The latest analyses demonstrate that intensive glucose lowering, once thought to have no benefit in CV outcomes, can reduce microvascular and macrovascular morbidities and CV mortality. Multifactorial interventions that combine intensive glucose lowering with BP and lipid lowering have also improved outcomes. However, the baseline BP of T2DM patients must be considered before initiating therapy, as it can counteract the beneficial impact on CV outcomes (72,73). Analyses from recent trials demonstrate that the glucose-lowering drug classes GLP-1 RAs and SGLT-2 inhibitors improved glycemic control and CV outcomes in comparison to established therapies, with the common mechanism between the classes of drugs being BP lowering. Similarly, nonpharmaceutical interventions in patients with T2DM, including physical activity and diet programs, efficiently reduce, not only blood glucose, but also BP and dyslipidemia, albeit with fewer side effects than with pharmacological interventions.

The majority of the evidence on lifestyle interventions does not go beyond the regulation of blood sugar or focuses on relatively short-term effects on CV risk markers. Additionally, existing evidence is negatively affected by underpowered studies, borderline significant results, or other methodological weaknesses (128,129). Consequently, there is a need for evidence on hard, longer-term CV outcomes resulting from lifestyle intervention in people with glucose dysregulation. The identified evidence on individual-level behavioral interventions supported existing recommendations on the content and delivery of behavior change interventions for diabetes prevention and management (40,74,75), but also supported the use of behavior change theory in intervention design, the need for high-quality delivery of person-centered delivery techniques, involvement of dietitians, self-monitoring of blood glucose (for people with diabetes), and the use of digital/mobile platforms to enhance intervention effectiveness. However, more research is needed to establish: 1) the cost-effectiveness of more or less intensive lifestyle interventions; 2) the effectiveness and cost-effectiveness of interventions to improve the maintenance of lifestyle changes; and 3) the

TABLE 2 Summary of Practical Recommendations for Service Design/Delivery and the Training of Health Care Professionals Involved in CVD Prevention

Intervention Level	Practical Recommendations
Pathophysiological	<ol style="list-style-type: none"> 1 Consider baseline BP before initiating intensive BP lowering in combination with intensive glucose lowering. 2 Consider the established patient CVD risk before deciding on pharmacological intervention.
Individual level	<ol style="list-style-type: none"> 1 Health promotion pathways should include lifestyle interventions targeting changes in diet, physical activity, and weight loss (for those who are overweight or obese) for people with diabetes or nondiabetic hyperglycemia (pre-diabetes), as well as medication adherence for those with diabetes. The intensity of interventions should be matched to the level of CV risk and the risk of T2DM (or its complications). 2 Maximizing effectiveness of individual-level interventions requires the commissioning of both interventions with evidence-based content (see Table 1) and the use of staff with the right competencies and training to effect high-quality delivery. 3 It is worth considering the development of "blended" interventions, where mobile-/internet-based technologies are used to share information between the patient and the clinician. This can facilitate helpful dialogue and help to facilitate a therapeutic self-management feedback loop including self-monitoring, feedback, and individually tailored problem-solving. eHealth interventions may be effective as stand-alone interventions for some people (those who have the capacity to be proactive, but should not be relied upon as a whole-population solution). 4 Although temporary changes in weight/lifestyle can have beneficial longer-term effects on blood glucose (particularly in the context of diabetes prevention), greater efforts are required to address the (ongoing) problem of relapse/reversion to prior habits. This may involve the provision of ongoing, regular maintenance contacts beyond the initial intervention period.
Population level	<ol style="list-style-type: none"> 1 The workplace setting is a highly attractive environment for population-level interventions because it incorporates social support in a stable environment. 2 There is a strong need for programs and trials providing longitudinal and more definitive data on the impact of population-level interventions on cardiometabolic risk factors and diseases.
General recommendations on competencies for training and standardizing health promotion care pathways	<ol style="list-style-type: none"> 1 Integration of existing CVD prevention and diabetes prevention, or diabetes self-management programs have the potential to improve care pathways. 2 Task-shifting in multidisciplinary care teams, especially involving community pharmacists and/or nurses, may improve clinical outcomes and may be of special benefit in regions where shortage of services limits availability of care. 3 CVD prevention service provider staff need to have training/be trained in the following competencies: Delivery of group- or individual-level behavior change interventions including: facilitation of key BCTs, including motivation-building using person-centered counseling techniques; making action plans; supporting self-monitoring (including the use of digital and blended-care approaches); facilitating barrier identification and problem-solving; and identifying and addressing social influences. 4 CVD prevention service managers need to have training/be trained in the following competencies: Understanding the evidence (as presented here) and being competent in commissioning/codesign of effective, evidence-based behavior change programs and training courses that will deliver the previously-described competencies. <p>Making the case to policy makers to acquire sufficient funding to deliver effective lifestyle interventions. Cutting corners when translating clinical intervention programs into real-world settings is likely to undermine effectiveness and cost-effectiveness (146).</p> <p>Designing stepped care pathways to ensure that the type/intensity of intervention is mapped to individual needs and capabilities.</p>
<p>The left column shows the focus of the individual review sections (pathophysiological and lifestyle interventions targeting the individual and the population); the right column shows practical recommendations derived from the evidence identified in each section; last row synthesizes the evidence into general recommendations on competencies for training and standardizing health promotion care pathways for the individual sections.</p> <p>BP = blood pressure; CVD = cardiovascular disease; eHealth = electronic health; other abbreviations as in Table 1.</p>	

effectiveness and cost-effectiveness of novel interventions to promote lifestyle changes (for instance, most existing interventions seem to focus on rational/planning and problem-solving strategies for supporting behavior change, rather than using novel methods to target impulsive, emotional, or social pathways to change [130-132]). Future interventions should incorporate text messaging, social media networking, and other digital health technology to encourage empowerment and self-management (133).

Although evidence on interventions aiming at individual behavior change is vast (Tables 1 and 2), population-based approaches employing multiple

mechanisms such as mandates, policies, programs, mass education, or built environmental changes have scarcely been tested for their impact on glycemic outcomes. For developing and maintaining new routines of healthy behavior the workplace setting provides a potentially supportive environment (134). There are ongoing programs and larger trials of policy, taxation, built environment, and other interventions focused on the broader population (99,135,136). Assessments of these programs and trials should provide longitudinal and more definitive data on the impact of these programs on cardiometabolic risk factors and diseases.

Population-based changes can be especially complicated to evaluate because of wider (and sometimes unintended) effects—for example, taxation programs might be considered socially regressive because they disproportionately affect lower socioeconomic classes (137). Other researchers recommend several possible areas for intervention at the policy and environmental levels, such as introducing liability for adverse health effects of food and beverage products in combination with individual-level prevention approaches (138).

The review identified evidence for the effectiveness of task shifting from medical doctors to community health workers and other community-based health practitioners such as nurses and pharmacists (121,125). This finding may be of tremendous benefit in rural areas and settings where a shortage of services and resources requires a shifting of responsibilities, such as prescribing following algorithms and protocols (127). Additionally, the potential for community-based multidisciplinary teams to increase effectiveness in both individual- and community-level interventions was observed (93). This is in line with current evidence highlighting significant improvements of multidisciplinary interventions in other areas of chronic disease management (139,140). Recent findings also indicate emerging evidence to support policy for chronic care management in primary care and community settings (141), especially because integrated care has proven to be cost-effective (142).

Taken altogether, the outcomes from every section support the potential for integrating prevention services. On a pathophysiological level, our research uncovers the benefits of blood glucose lowering for patients with T2DM in order to lower CV risk and thereby prevent CVD. For lifestyle interventions targeting individual behavior, the logic is less straightforward, yet nevertheless needs to be considered. Although individual-level interventions for behavior change directly reduce blood glucose, they indirectly target CVD risk. By promoting physical activity and diets, CVD risk factors, such as increased blood glucose and weight, are addressed. Population-wide strategies also reduce CVD risk both directly and indirectly: interventions seeking to reduce adult obesity in people with T2DM thereby also address a major risk factor for CVD. Yet, there is also evidence supporting the effectiveness of physical activity implemented in a workplace setting in reducing hazardous cardiometabolic outcomes. Despite the identified lack of good-quality evidence on CV risk factor improvement via integrated care (118), incorporating community-based pharmacists into

multidisciplinary care teams can reduce the burdens of CVD and T2DM (93).

Combining the results derived from the single sections suggests integrating future services and policy efforts to develop standardized care pathways covering diabetes prevention, diabetes management and CVD prevention. Focusing on the entire pathway of CVD and diabetes prevention, management and care is also supported by the Organisation for Economic Cooperation and Development health policy studies on CVD and diabetes (143), as well as evidence-based recommendations given by the European guidelines on CVD prevention in clinical practice (144).

STRENGTHS AND LIMITATIONS. This study used robust, high-quality systematic reviewing methods to generate an overview of evidence on glucose regulation. Systematic umbrella reviews are helpful to summarize complicated and vast amounts of research to efficiently inform decision makers in the health sector, such as policy makers and clinicians (36).

A focus on these high-quality data limits the risk of overlooking major trends on a given subject. However, there are some limitations that need to be acknowledged. Some relevant research may not have been included in meta-analyses, despite being of high quality. Such selection bias may have arisen from limitations in the search terms and range of databases searched. Further selection bias might arise from the choice of relevant primary studies by the authors of the reviews and meta-analyses included. As the search for systematic reviews and meta-analyses on population-wide interventions has shown, experimental trial designs are less commonly applied (and may be less appropriate) in the field of community-based intervention, either due to ethical concerns or simple economic barriers of feasibility. Hence, including observational studies or quasiexperimental designs might have generated additional insights. To include the most up-to-date evidence, the search was limited to the latest systematic reviews and meta-analyses published during a narrow period of time (early 2016 to late 2017). Finally, section 4 did not apply an individual search strategy but relied on reviews identified by the other 3 sections.

CONCLUSIONS

Overall, this review has outlined the state of the art in relation to the field of blood glucose regulation and suggests that this evidence can be used to extend existing guidance for CVD prevention (Table 2).

CV prevention services should consider the regulation of blood glucose as a key target for intervention and adopt the recommendations for effective

intervention and service delivery described in this review as well as in existing evidence-based practice guidelines. Addressing the individual needs of patients is key for CV prevention programs and should take into account pathophysiological mechanisms and aspects influencing individual behavior change, both on the individual as well as the environmental level. Multidisciplinary teams (including pharmacists, nurses, or community health workers) should be formed to deliver multicomponent interventions in community-based settings.

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KEY WORDS blood glucose, diabetes mellitus, diet, exercise, health behavior, umbrella review, weight loss

APPENDIX For supplemental tables, please see the online version of this paper.