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The Relationship of Digestible Carbohydrate Intake With Cardiovascular Disease, Type 2 Diabetes, Obesity, and Body Composition

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The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

Technical Expert Panel. In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who provided input to this report follows: To be provided in the final version of the report

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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The Relationship of Digestible Carbohydrate Intake With Cardiovascular Disease, Type 2 Diabetes, Obesity, and Body Composition

Abstract

Background: Epidemiological studies have shown inconsistent findings regarding the effect of dietary digestible carbohydrate intake on the risk of cardiovascular disease and type 2 diabetes (T2D). Synthesis of such evidence is important for determining the Dietary Reference Intakes (DRI) for carbohydrates, which can have consequences on incidence and morbidity of chronic conditions.

Methods: Two systematic reviews were conducted, one addressing cardiovascular outcomes and the second addressing incidence of T2D, body weight and composition. We searched several databases from January, 2000 to October, 2023. We also conducted gray literature search and reference mining. Eligible studies evaluated the outcomes of interest in healthy individuals over 2 years old and isolated the effect of digestible carbohydrate intake from other macronutrients in grams per day or percent of total energy intake. Random-effects dose-response meta-analyses were conducted when feasible.

Results: The systematic review on cardiovascular outcome included 21 prospective cohort studies with1,277,621 participants. The majority of the studies reported inadequate confounding adjustment (73%) and were deemed to have serious risks of bias (80%). No eligible studies evaluated children aged <18 years. The association between digestible carbohydrate intake and cardiovascular outcomes was nonlinear and was supported by low strength of evidence. When carbohydrate intake was analyzed as the percentage of total energy intake, the risk of incident cardiovascular disease significantly increased when carbohydrate intake exceeded 65% total energy intake, compared with the carbohydrate intake reference level of 50% total energy intake. The lowest risk was at a carbohydrate intake level of 50% total energy intake. The risk of incident coronary heart disease increased starting at a carbohydrate intake level of 45% total energy intake. When carbohydrate intake was analyzed as grams per day, the risk of incident cardiovascular disease significantly increased when carbohydrate intake exceeded 300 grams per day, compared with the carbohydrate intake reference level of 300 grams per day. The lowest risk was at a carbohydrate intake level of 250 grams per day. The risk of incident coronary heart disease increased starting at 250 grams per day of carbohydrates. The nonlinear relationships were overall similar based on sex or geographic location but with variable intake range associated with the lowest risk. Higher carbohydrate intake was associated with lower levels of high-density lipoprotein- cholesterol (HDL-C) and higher levels of triglycerides.

The systematic review on diabetes and body composition included 17 studies with 463,228 participants. The majority of the studies reported inadequate confounding adjustment (79%) and were deemed to have serious risks of bias (92%). No eligible studies evaluated children aged <18 years. The association between carbohydrate intake and incident T2D was nonlinear and was supported by low strength of evidence. Analyzing carbohydrate intake as a percentage of total energy intake showed a gradual reduction in the risk of incident T2D up to 45% total energy

intake. The risk then plateaued between 45% and 55% total energy intake before rising with higher carbohydrate intake levels. Similarly, analyzing carbohydrate intake in grams per day revealed a gradually reduced risk up to 270 grams per day of carbohydrates, followed by a plateau between 270–350 grams per day of carbohydrates and increased risk after 350 grams per day of carbohydrates.

The evidence was insufficient to determine an association between carbohydrate intake and weight or body composition. The nonlinear relationships were overall similar based on sex but with variable intake range associated with the lowest risk. Very few studies evaluated intermediate outcomes.

Conclusion: Dose-response meta-analyses suggest a nonlinear relationship between the intake of digestible carbohydrates and cardiovascular disease and incident T2D. These associations appear to be U-shaped and suggest certain ranges of carbohydrate intake that were associated with the lowest risk. Such ranges can help in establishing future DRI for carbohydrates, which can have important consequences on incidence and morbidity of chronic conditions and public health.

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Main Points

Systematic review on risk of cardiovascular disease

- A majority of the included studies reported inadequate confounding adjustment and were deemed to have serious risk of bias.
- No eligible studies evaluated children aged <18 years.
- The association between digestible carbohydrate intake and cardiovascular outcomes was nonlinear and supported by low strength of evidence.
- When digestible carbohydrate intake was analyzed as the percentage of total energy intake, the risk of incident cardiovascular disease (CVD) significantly increased when carbohydrate intake exceeded 65% total energy intake, compared with the carbohydrate intake reference level of 50% total energy intake. The lowest risk was at a carbohydrate intake of 50% total energy intake. The risk of incident coronary heart disease increased starting at 45% total energy intake.
- When digestible carbohydrate intake was analyzed as grams per day, the risk of CVD significantly increased when carbohydrate intake exceeded 300 grams per day of carbohydrates, compared with the reference level of 300 grams of carbohydrates per day. The lowest risk was at a carbohydrate intake of 250 grams per day. The risk of incident coronary heart disease increased starting at 250 grams per day of carbohydrates.
- The risk of CVD-related mortality was U shaped and might be lowest with an intake 250–300 grams of carbohydrates per day.
- The risk of stroke was not significantly associated with carbohydrate intake and had a less defined dose-response relationship. The risk increased when carbohydrate intake exceeded 50% total energy intake.
- The nonlinear relationships were overall similar based on sex or geographic location but with variable carbohydrate intake ranges associated with the lowest risk.

Systematic review on risk of type 2 diabetes, growth, size, and body composition

- A majority of the included studies reported inadequate confounding adjustment and were deemed to have serious risk of bias.
- No eligible studies evaluated children aged <18 years.
- The association between carbohydrate intake and incident type 2 diabetes (T2D) was nonlinear and supported by low strength of evidence.
- When digestible carbohydrate intake was reported as the percentage of total energy intake, the risk of incident T2D gradually decreased from the lowest carbohydrate intake until 45% total energy intake, remained relatively flat between 45% and 55% total energy intake, and increased gradually from 55% total energy intake.
- When digestible carbohydrate intake was reported as grams per day, the risk of incident T2D gradually decreased from the lowest carbohydrate intake until 270

grams per day, remained relatively flat between 270 to 350 grams per day of carbohydrates, and increased gradually from 350 grams per day of carbohydrates.
- The evidence was insufficient to determine an association between carbohydrate intake and weight or body composition.
- The nonlinear associations were overall similar based on sex but with variable carbohydrate intake ranges associated with the lowest risk.
- Very few studies evaluated surrogate outcomes.

Background and Purpose

Despite fluctuating trends in mortality rates in the last few decades,[1-3] CVD remains the leading cause of death in the United States,[4] and the incidence of T2D, hypertension, dyslipidemia, and obesity is expected to increase.[5] Personal and cultural dietary habits have been identified as potential risk factors associated with CVD, particularly carbohydrate intake.[6]

Healthcare authorities and international health organizations have published guidelines for nutrient recommendations, including recommendations for optimal consumed energy percentage or quantity in the form of carbohydrates intake.[7-13] Despite some inconsistencies in the methodologies and contexts, the recommendations are generally similar and recommend carbohydrate intake to be between 45% and 65% of total energy consumption. The Dietary Reference Intakes (DRI) for carbohydrates were published in 2005 and were essentially determined based on the brain's estimated requirement of glucose in different age groups, taking into consideration increased physiological requirements during times of growth, pregnancy, and breastfeeding. For children older than 1 year and adults of all age groups and sexes, the Recommended Dietary Allowance (RDA) of carbohydrates is set as 130 grams per day. The RDA changes to 175 grams per day during pregnancy and 210 grams per day during breastfeeding. It is worth noting that the average consumption of carbohydrates differs substantially from the RDA, even in healthy individuals on balanced diets.[14, 15] Furthermore, in a typical 2000 to 2200 calorie diet that is considered socially and medically appropriate, the acceptable macronutrient distribution range (AMDR) of carbohydrate varies widely between countries and recommending organizations and can be between 40% to75% total energy intake,[16] which translates to approximately 200–375 grams per day of carbohydrates.

Since the 2005 DRI publication in the United States and Canada, there has been significant growth in the body of evidence. Multiple long-term studies have been conducted that provide insight into the role of digestible carbohydrates in the development (or prevention) of chronic conditions. Therefore, future considerations for DRI should aim to incorporate risk reduction of chronic disease.

Questions regarding the association between digestible carbohydrate intake and the risk of cardiovascular disease and the risk of T2D have been debated with conflicting results due to the presence of numerous confounding factors. With T2D being a major risk factor for CVD and CVD mortality, it is important to identify the association between digestible carbohydrate intake and both of these chronic conditions.

We conducted two systematic reviews to evaluate (1.) the association between dietary digestible carbohydrate intake and the incidence of cardiovascular disease and (2.) the association between dietary digestible carbohydrate intake and the incidence of T2D and the effect on growth, size, and body composition. These two reviews intend to inform the upcoming U.S. and Canadian government DRI guideline about dietary digestible carbohydrate intake.

Methods

We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[17] The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[18] The study protocol was published on AHRQ website (https://effectivehealthcare.ahrq.gov/products/effect-dietary-digestible and https://effectivehealthcare.ahrq.gov/products/risk-cardiovascular-disease) and was registered to the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42024494567 and CRD42024496101). The literature search spanned from January1, 2000 to October 24, 2023.

Results

Systematic Review of the Effect of Dietary Digestible Carbohydrate Intake on Risk of Cardiovascular Disease

Twenty-one prospective cohort studies with 1,277,621 participants were included. The median age of the participants was 51.7 years (range: 24.8–57.9 years); 59.90% were women. Six studies were conducted in Europe (Finland, the United Kingdom, Sweden, Germany, Italy, France, Denmark, Spain, the Netherlands); eight in Asia (Japan, Korea, China, and Singapore), one in Australia, five in the United States, and one on multiple continents. The median followup was 10.7 years, ranging from 1 to 32 years. We found no eligible studies in children. Detailed results can be found in the Results section of the main report.

Cardiovascular Disease

Seventeen studies with 1,264,870 participants evaluated the association between digestible carbohydrate intake and the incidence of CVD. The median age of the participants was 52.5 years (range: 24.8–57.9 years). The range of digestible carbohydrate intake was from 33.4% to 79.0% total energy intake for studies reporting the percentage of total energy intake and from 138.8 to 368.7 grams per day of carbohydrates for studies reporting grams per day.

Nine out of 17 studies reported a significant association between digestible carbohydrate intake and incident CVD (three suggested reduction in risk, and six suggested increased in risk). We observed a nonlinear U-shaped dose response relationship. Analyzing carbohydrate intake as a percentage of total energy intake showed a gradual decrease in the risk of incident CVD up to 50% total energy intake, followed by an increase at higher carbohydrate intake levels. When compared with a carbohydrate intake reference level of 50% total energy intake, a digestible carbohydrate intake level exceeding 65% was associated with a significantly increased risk of incident CVD. Similarly, analyzing carbohydrate intake in grams per day revealed a steady decline in CVD risk up to 250 grams per day of carbohydrates, with an increased risk at higher carbohydrate intake levels. Exceeding the carbohydrate intake reference level of 300 grams per day was associated with a significantly increased risk of incident CVD.

Coronary Heart Disease

Nine studies with 676,794 participants evaluated the risk of incident CHD. The median age of the participants was 48.0 years (range: 24.8–57.9 years). The range of digestible carbohydrate intake was from 33.4% to 79.0% total energy intake for studies reporting the

percentage of total energy intake and from 191.6 to 311.4 grams per day of carbohydrates for studies reporting grams per day.

Five studies reported a significantly increased risk of CHD. The linear dose-response meta-analysis showed a significant association between the risk of incident CHD and digestible carbohydrate intake (per 10% total energy intake increase: RR=1.17; 95% CI: 1.02 to 1.34). We also observed a nonlinear dose-response relationship. Analyzing carbohydrate intake as a percentage of total energy intake showed a relatively flat risk of incident CHD up to 45% total energy intake. However, the risk rose sharply when carbohydrate intake exceeded 45% total energy intake. Exceeding the carbohydrate intake reference level of 50% total energy intake was associated with a significantly increased CHD risk. Similarly, analyzing carbohydrate intake in grams per day revealed a flat CHD risk up to 250 grams per day of carbohydrates, followed by a sharp rise in risk at higher carbohydrate intake levels.

Cardiovascular Disease-Related Mortality

Five studies with 330,774 participants reported CVD-related mortality. The median age of the participants was 50.3 years (range: 48.6–54.7 years). The range of digestible carbohydrate intake was from 40.5% to 77.2% total energy intake for studies reporting the percentage of total energy intake and from 138.8 to 368.7 grams per day of carbohydrates for studies reporting grams per day.

Only one study reported a significantly negative association between carbohydrate intake and CVD-related mortality. We observed a U-shaped nonlinear dose-response relationship. Analyzing carbohydrate intake as a percentage of total energy intake showed a gradual decrease in the risk of CVD-related mortality up to 55% total energy intake, after which the risk increased. Similarly, analyzing carbohydrate intake in grams per day showed a reduced risk up to 260 grams per day of carbohydrates, followed by an increased risk at higher carbohydrate intake levels. Compared with the carbohydrate intake reference level (300 grams per day), digestible carbohydrate intake below 215 grams per day was associated with significantly increased risk of CVD-related mortality.

Stroke

Nine studies with 338,554 participants reported the association between digestible carbohydrate intake and the risk of incident stroke. The median age of the participants was 50.0 years (range: 24.8–57.9 years). The range of digestible carbohydrate intake was from 32.6% to 77.2% total energy intake for studies reporting percentage of total energy intake and from 221.9 to 368.7 grams per day of carbohydrates for studies reporting grams per day.

All but one study reported no significant association between digestible carbohydrate intake and the risk of incident stroke. Nonlinear dose-response meta-analyses suggested that the risk of incident stroke was generally flat until 50% of total energy intake and then the risk gradually increased with higher carbohydrate intake.

Subgroup Analysis based on Sex and Geographic Locations

We found no significant linear dose-response association between carbohydrate intake and incident CVD in either men or women. Similar nonlinear U-shaped dose-response relationships were found in women and men with the lowest risk at 225 grams per day for women and 280 grams per day for men.

Nonlinear dose-response relationship showed a similar U-shaped relationship in studies conducted in Western Countries and East Asia, although studies conducted in Western Countries suggested lower carbohydrate intake levels at the lowest CVD risk (225 grams per day: RR=0.91, 95% CI: 0.87 to 0.96), compared with those conducted in East Asia (285 grams per day: RR=1.00, 95% CI: 0.97 to 1.04).

Strength of Evidence for Cardiovascular Outcomes

Evidence Summary Table 1 shows the strength of evidence for cardiovascular outcomes.

Evidence Summary Table 1. Strength of evidence for cardiovascular outcomes

Outcome	Effect	SOE	Rationale
Incident cardiovascular disease	17 studies with 1,264,870 participants (median age of 52.5 years) • Nonsignificant association with carbohydrate intake (per 10-gram increase: RR=0.99; 95% CI: 0.97 to 1.02; per 10% E increase: RR=1.03; 95% CI: 0.96 to 1.09). • U-shaped nonlinear association. • Highest association was observed when intake exceeded 65% E; lowest risk with intake at 50% E. • Highest association was observed when intake exceeded 300 grams per day of carbohydrates; lowest risk with intake at 250 grams per day of carbohydrates.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Serious risk of bias.
Incident coronary heart disease	9 studies with 676,794 participants (median age of 48.0 years) • Significant association with carbohydrate intake (per 10% E increase: RR=1.17; 95% CI: 1.02 to 1.34). • U-shaped nonlinear association. • Risk significantly increased starting at 45% E. • Risk significantly increased starting at 250 grams per day of carbohydrates.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Serious risk of bias.

Outcome	Effect	SOE	Rationale
Cardiovascular disease-related mortality	5 studies with 330,774 participants (median age of 50.3 years) • Nonsignificant associations with carbohydrate intake (per 10-gram increase: RR=1.00; 95% CI: 0.97 to 1.02; per 10% E increase: RR=1.00; 95% CI: 0.97 to 1.04). • U-shaped nonlinear association. • Significantly increased risk below 215 grams per day of carbohydrates.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Wide confidence intervals or risk estimates across the majority of the intake range. • Serious risk of bias.
Incident stroke	9 studies with 338,554 participants (median age of 50.0 years) • All but one study showed nonsignificant association. • Dose-response meta-analysis also showed nonsignificant associations. • Less defined nonlinear dose-response association with increase in risk at 50% E.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Wide confidence intervals or risk estimates across the majority of the intake range. • Serious risk of bias

Abbreviations: % E = percentage of total energy intake; CI = confidence interval; RR = relative risk; SOE = strength of evidence

Systematic Review of the Effect of Dietary Digestible Carbohydrate Intake on Risk of Type 2 Diabetes, Growth, Size, and Body Composition

Fifteen prospective cohort studies and two randomized controlled trials were included. The median age of the participants was 49.3 years (range: 31.1–63.3 years); 75.63% were women. Six studies were conducted in Europe (Finland, the United Kingdom, Sweden, Germany, Italy, France, Denmark, Spain, the Netherlands), five in East Asia (Japan, Korean, China), one in the Middle East (Iran), two in Australia, and three in the United States. The median followup was 10.0 years, ranging from 16 weeks to 20 years. We found no eligible studies in children. Detailed results can be found in the Results section of the main report.

Type 2 Diabetes and Gestational Diabetes

No study evaluated incident gestational diabetes. Eleven studies with 452,586 participants evaluated incident T2D. The median age of the participants was 52.5 years (range: 36.1–58.0 years). The reported range of digestible carbohydrate intake was from 149.8 to 432.7 grams per day of carbohydrates for studies reporting grams per day or from 28.3% to 80.1% total energy intake for studies reporting percentage of total energy intake.

One study reported a significantly increased risk of T2D with increased carbohydrate intake, and two studies reported significantly reduced risk. The nonlinear dose-response analyses reflected a U-shaped association. Analyzing carbohydrate intake as a percentage of

total energy intake showed a gradual reduction in the risk of incident T2D up to 45% total energy intake. The risk then plateaued between 45% total energy intake and 55% of total energy intake before rising with higher carbohydrate intakes. Similarly, analyzing carbohydrate intake in grams per day revealed a gradually reduced risk up to 270 grams per day of carbohydrates, followed by a plateau between 270 to 350 grams per day of carbohydrates and increased risk after 350 grams per day of carbohydrates.

Growth, Size, and Body Composition

Seven studies with 20,216 participants reported the association between digestible carbohydrate intake and changes in weight. The median age of the participants was 51.2 years (range: 36.4–61.0 years). Digestible carbohydrate intake ranged from 35.2% to 63.2% total energy intake for studies reporting percentage of total energy intake and from 156 to 393 grams per day of carbohydrates for studies reporting grams per day.

Two studies reported significantly reduced risk of weight gain with increased carbohydrate intake; one study reported significantly increased risk, and one study found no significant association.

Subgroup Analysis based on Sex and Geographic Locations

We found similar U-shaped nonlinear dose-response relationships in men and women, with the lowest risk at 48% total energy intake.

Studies conducted in Western Countries and East Asia showed different patterns of nonlinear dose-response relationships, possibly due to different ranges of carbohydrate intake: in studies conducted in Western Countries, a U-shaped relationship was observed with initial reduction and then increased risk with increased intake, while in East Asian studies, there was initially increased risk, and then stable risk.

Strength of Evidence for T2D and Body Weight

Evidence Summary Table 2 shows strength of evidence for T2D and body weight.

Evidence Summary Table 2 . Strength of evidence of type 2 diabetes and body weight

Outcome	Effect	SOE	Rationale
Incident type 2 diabetes	11 studies with 452,586 participants (median age of 52.5 years) • Nonsignificant associations with carbohydrate intake (per 10-gram per day increase: RR=0.96; 95% CI: 0.90 to 1.04; per 10% E: RR=0.93; 95% CI: 0.78 to 1.11). • Nonlinear association. • The risk reduced from low level of carbohydrate intake till until 45% E, remained relatively flat between 45% and 55% E, and increased gradually from 55% E. • The risk reduced from low level of carbohydrate intake till until 270 grams per day, remained relatively flat between 270 grams per day of carbohydrates and 350 grams per day of carbohydrates, and increased gradually from 350 grams per day of carbohydrates.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Wide confidence intervals or risk estimates across most of the intake range. • Serious risk of bias.
Body weight	7 studies with 20,216 participants (median age of 51.2 years) • Inconsistent findings (in 2 reduced risk of weight gains, in 1 increased, and in 4 nonsignificant change).	Insufficient SOE	• Very serious concern about inconsistency. • Serious risk of bias.

Abbreviations: %E=percentage of total energy intake; CI = confidence interval; RR = relative risk; SOE = strength of evidence

Limitations

The included studies adopted a wide range of dietary assessment methods, most commonly using food frequency questionnaires (FFQs). The validity of these instruments across the various geographic locations of the included studies is unclear. The studies also used various recall periods, including longer than 3 months, which increases the risk of measurement bias.

A major challenge in nutrition research is how to account for other nutrients that are co-existent in food. The whole food matrix, with its associated micronutrients and phytochemicals, is what is consumed and not individual macronutrients, and therefore drawing firm conclusions about any macronutrient can be difficult. In this systematic review, we extracted and synthesized results from the most adjusted model of individual studies, with the intention to control macronutrients to the fullest. However, most of the included studies only partially performed these adjustments. We were also unable to discern differences in carbohydrate quality, for example between simple carbohydrates (e.g., fructose from sugar-sweetened beverages) and more complex ones (e.g., starches from corn and potatoes). This limitation is in part because of the varied methods for reporting dietary intake. Additionally, there is still no accepted consensus on how to define carbohydrate quality, although several proposals have been put forward. Variations in food consumption patterns and cooking approaches across the various locations of the available studies limits generalizability of results to other locations.

Length of study followup was also variable, ranging from 16 weeks to 32 years. Studies with short followup did not account for the variable rates of disease progression and may have underestimated the influence of digestible carbohydrate consumption in the long term. A rigorous long-term prospective study in a controlled feeding environment would answer

these questions reliably, but due to practicality, it is unlikely to be feasible. As intake over a lifespan may influence the development of these chronic diseases, studies following individuals throughout their entire lifespans would be ideal. However, a more feasible approach may be followup for at least 5-10 years. Such studies should also monitor weight stability and weight changes in addition to other lifestyle factors.

As studies getting to the outcome of interest are challenging given the long-term nature required, shorter term studies looking at surrogate markers will continue to be more feasible. However, very few studies reported intermediate outcomes or surrogate outcomes (e.g., low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, glucose tolerance), partially due to lack of eligible clinical trials. Lastly, it is important to acknowledge the limitations of study-level meta-regression and dose-response meta-analysis, such as ecological bias, and particularly with a small sample size, the potential for large relative estimates that may not be biologically plausible.

Implications and Conclusions

Dose-response meta-analyses suggest a nonlinear relationship between the intake of digestible carbohydrates, CVD, and incident T2D. These associations appear to be U-shaped. Evaluation of the shapes of these associations demonstrates certain ranges of carbohydrate intake that were associated with the lowest risk. These ranges can aid in developing future DRIs for carbohydrates, which can have important consequences on the incidence and morbidity of chronic conditions and public health. The available literature suffers from serious limitations due to inadequate adjustment of confounding and an inability to clearly isolate the effect of macronutrients from each other. The current results are subject to ecological bias because they are derived from aggregate data.

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1.Introduction

1.1 Background

1.1.1. The Effect of Dietary Digestible Carbohydrate Intake on Risk of Cardiovascular Disease

Despite fluctuating trends in mortality rates in the last few decades,[1-3] cardiovascular disease (CVD) remains the leading cause of death in the United States,[4] with a projected future increase in CVD risk factors, including type 2 diabetes (T2D), hypertension, dyslipidemia, and obesity.[5] Personal and cultural dietary habits have been identified as potential risk factors associated with CVD, particularly carbohydrate intake.[6]

Healthcare authorities and international health organizations have published guidelines for nutrient recommendations, including recommendations for optimal consumed energy percentage or quantity in the form of carbohydrates intake.[7-13] Despite some inconsistencies in the methodologies and contexts, the recommendations are generally similar and recommend carbohydrate intake to be between 45% and 65% of total energy consumption, except for the World Health Organization (WHO) guidelines that recommend up to 75% of the energy to be from carbohydrates.[14] The Dietary Reference Intakes (DRI) for carbohydrates were published in 2005 and were essentially determined based on the brain's estimated requirement of glucose in different age groups, taking into consideration increased physiological requirements during times of growth, pregnancy, and breastfeeding. For children older than 1 year and adults of all age groups and sexes, the Recommended Dietary Allowance (RDA) of carbohydrates is set as 130 grams per day. The RDA changes to 175 grams per day during pregnancy and 210 grams per day during breastfeeding. It is worth noting that the average consumption of carbohydrates differs substantially from the RDA, even in healthy individuals on balanced diets.[15, 16] Furthermore, in a typical 2000 to 2200 calorie diet that is considered socially and medically appropriate, the acceptable macronutrient distribution range (AMDR) of carbohydrates varies widely between countries and recommending organizations and can be between 40% to 75% total energy intake, which translates to approximately 200 to 375 grams per day of carbohydrates.[14] Questions regarding the association between digestible carbohydrate intake and the risk of CVD have been debated with conflicting results due to the presence of numerous confounding factors. However, there has been significant growth in the body of evidence regarding the effect of carbohydrates on CVD (e.g., all cardiovascular events, risk of stroke, and risk of coronary heart disease) since the publication of the recommended DRI in the United States and Canada.[17-19] Some studies suggested that carbohydrate-rich diets may be associated with a higher risk of stroke and overall cardiovascular events.[18, 20] On the other hand, an association between high carbohydrate diet and coronary heart disease was not clearly found.[18, 20, 21]

In addition, a high carbohydrate diet has been shown in multiple observational studies to be associated with higher triglycerides levels and lower high-density lipoprotein cholesterol (HDL-C).[22-25] Some of these studies showed a decrease in low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) levels in high carbohydrate diets[22-24] but with an increase in TC to HDL-C ratio.[23] In addition, some data support a positive effect of low carbohydrate diet on blood pressure.[26, 27] To date, the effect of digestible carbohydrate intake on blood pressure as a risk factor for CVD has not been clearly determined.[28, 29]

1.1.2 The Effect of Dietary Digestible Carbohydrate Intake on Risk of Type 2 Diabetes, Growth, Size, and Body Composition

The DRI for carbohydrates was last released in 2005[15], and in the decades since, interest and available data in this field have grown tremendously. DRI for carbohydrates can be linked to chronic diseases such as diabetes and obesity, which affect the lives of millions of people in the United States and globally. Since these conditions become more prevalent with age, they are likely caused by a cumulative exposure to external factors, such as nutrient intake.

Carbohydrates are organic compounds that are made up of molecules of carbon, hydrogen, and oxygen, which are absorbed as monosaccharides (e.g., glucose) before they can be used as energy for human cellular function. As such, their pathophysiological role in T2D and other forms of glucose intolerance has been of interest for a long time. Longitudinal nutritional studies suggest that higher intake of high-quality carbohydrates as defined by whole grain, high fiber, and, in some studies, low glycemic load, in addition to other lifestyle factors, can lead to a 90% risk reduction in the development of T2D.[30, 31] These studies were criticized for inadequate adjustment for confounders, such as weight loss and fat consumption, which often accompany dietary changes.

Obesity, being overweight and having excess body fat/adipose tissue are risk factors of the development of T2D. Although some studies have proposed that the type of calorie consumed (in this case calories of carbohydrate origin) may influence energy partitioning, this is still not widely accepted to be true.[32, 33] Hence, an important question to answer is whether carbohydrate consumption influences body weight regulation and body composition, independent of its calorie content.

In infants and children, carbohydrate intake is critical for growth and development. Glucose is the main oxidative fuel of brain cells, and carbohydrate intake is linked to cognition.[34] Carbohydrate intake influences metabolism and can minimize the protein cost of gluconeogenesis and irreversible protein and nitrogen loss, and carbohydrate intake prevents ketosis and its consequences, affecting growth. Population-based studies in children link carbohydrate intake and its subtypes, such as monosaccharides and disaccharides, with changes in serum lipids.[35] Furthermore, some evidence exists associating sugar-rich (particularly fructose rich) diet with increased risk for nonalcoholic fatty liver disease (NAFLD) in children who have obesity.[36, 37] Unfortunately, most studies about carbohydrates intake and energy metabolism have been conducted in adults and newborns, the latter being in a transitional phase of metabolic adaptation. Thus, studies performed in children between one year and puberty are sparse.[38]

1.2 Purpose and Scope of the Review

We conducted two systematic reviews to evaluate (1.) the association between dietary digestible carbohydrate intake and the incidence of CVD and (2.) the association between dietary digestible carbohydrate intake and the incidence of T2D and effect on growth, size, and body composition. These two reviews intend to inform the upcoming U.S. and Canadian government DRI guideline about dietary digestible carbohydrate intake.

2. Methods

2.1 Review Approach

The two systematic reviews follow the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[39] The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[40] A panel of Technical Experts provided high-level content and methodological expertise throughout development of the review protocol. The final protocols are registered in the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42024494567 and CRD42024496101) and posted on the EHC website at https://effectivehealthcare.ahrq.gov/products/effect-dietary-digestible and https://effectivehealthcare.ahrq.gov/products/risk-cardiovascular-disease.

2.2 Key Questions

The Key Questions (KQ) for the systematic review of the effect of dietary digestible carbohydrate intake on risk of cardiovascular disease (CVD) and the risk of type 2 diabetes (T2D), growth, size, and body composition can be found below.

KQ: What is the association between dietary digestible carbohydrate intake and the incidence of cardiovascular disease?

KQ: What is the association between dietary digestible carbohydrate intake and the incidence of type 2 diabetes (T2D) and effect on growth, size, and body composition (i.e., obesity, overweight, body weight and composition)?

2.3 Study Selection

2.3.1 Search Strategy

We searched several bibliographic databases, including Embase® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE® Daily, MEDLINE®, Cochrane Central Register of Controlled Trials, Ovid® Cochrane Database of Systematic Reviews, and Scopus® from January 1, 2000 to October 23, 2023. We also searched the U.S. Food and Drug Administration, ClinicalTrials.gov, Health Canada, U.K. Medicines and Healthcare Products Regulatory Agency (MHRA), conference proceedings, patient advocate group websites, and medical society websites. We conducted reference mining of existing systematic reviews/meta-analyses, completed trials identified from clinical trial registries, and relevant primary studies to identify additional literature. In addition, a Supplemental Evidence and Data for Systematic Reviews (SEADS) portal, which collected additional study-specific information from industry stakeholders, professional societies, and researchers was open from January 16, 2024, to February 15, 2024, was created on the Effective Health Care website and publicized on the Federal Register. The literature search strategies for the two systematic reviews were developed by an experienced medical librarian and peer-reviewed by an independent information specialist.

The same medical librarian conducted the literature search. The detailed search strategies are listed in Appendix A.

2.3.2 Inclusion and Exclusion Criteria

2.3.2.1 Systematic Review of the Effect of Dietary Digestible Carbohydrate Intake on Risk of Cardiovascular Disease

The eligible studies for the KQ had to meet all of the following criteria: (1) general population over 2 years old, (2) reported total dietary digestible carbohydrate intake and isolated effect or association of digestible carbohydrate intake from the effects of other macronutrients (e.g., adjustments of other macronutrients), (3) compared different total dietary digestible carbohydrate intake level(s), (4) reported outcomes of interest (CVD or intermediate outcomes), (5.) followed participants at least 4 weeks, (6) were randomized controlled trials (RCTs), nonrandomized controlled trials, prospective cohort studies, or nested case-control studies, (7) were published in English as peer reviewed full text publication, and (8) were published after the year 2000 to focus on studies that were not included in the 2005 DRI for carbohydrates. We excluded studies with infants or children under the age of 2 years old, participants who had diseases/health-related conditions that can affect carbohydrate absorption or metabolism, including cancer and malabsorption syndromes; participants were already diagnosed with the endpoint outcomes of interest (i.e., CVD), participants who intended to reduce weight or receive treatments for being overweight or having obesity through energy restriction or hypocaloric diets for the purposes of treating additional or other medical conditions; participants who were determined to be undernourished, underweight, stunted, or wasted; or participants who were pre-bariatric or post-bariatric surgery. We also excluded studies that did not describe the entire macronutrient distribution of the diet, provided carbohydrates via infusions (rather than the GI tract), evaluated only the quality or individual sources of carbohydrates, or included food products or dietary supplements not widely available in the United States. Studies about hypertensive disorders during pregnancy and/or lactation were not evaluated. The detailed inclusion and exclusion criteria for the KQ are listed in Table 1.

2. Methods

Table 1. Inclusion and exclusion criteria by population, intervention, comparator, outcome, timing, setting/study design (PICOTS) for systematic review of cardiovascular disease

PICOTS Elements	Inclusion Criteria	Exclusion Criteria

Population	• General population, including participants who are determined to be overweight/obese, women who are pregnant or lactating
	• Age of participants
	  ○ Between 2 years and 9 years (before puberty)
	  ○ Between 9 yearsand17 years
	  ○ 18 years and older
		• Participants with diseases/health-related conditions that impact carbohydrate absorption or metabolism, cancer, and malabsorption syndromes
		• Participants hospitalized with an illness or injury
		• Participants with the endpoint outcomes of CVD (i.e., studies that aim to treat participants already been diagnosed with the endpoint outcomes of interest)
		• Participants who intend to reduce weight or receive treatments for being overweight and having obesity through energy restriction or hypocaloric diets for the purposes of treating additional or other medical conditions
		• Participants who are determined to be undernourished, underweight, stunted, or wasted
		• Participants who are pre-bariatric or post-bariatric surgery
		• People younger than 2 years old

Interventions	• Total dietary digestible carbohydrate intake from foods, beverages, and dietary supplements ○ Total dietary digestible carbohydrate intake defined as collective starch and sugar intake; carbohydrate intake not including dietary fiber • A dietary pattern that quantifies the intake of total dietary digestible carbohydrates and allows the isolation of the effect of carbohydrate intake from the effect of the intake of other macronutrients	• Studies that do not specify the amount of total digestible carbohydrate intake (e.g., studies that only report type or source of digestible carbohydrate) • Studies that do not describe the entire macronutrient distribution of the diet (i.e., studies that do not report total digestible carbohydrate, total fat, and total protein contents of experimental or baseline diets) • Studies that only assess digestible carbohydrate intake via infusions (rather than the GI tract) • Studies that primarily measure postprandial responses, as opposed to longer term studies • Studies that examine food products or dietary supplements not widely available to U.S. consumers • Multi-component interventions that do not isolate the effect or association of digestible carbohydrate

2. Methods

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Comparators	• Different total dietary digestible carbohydrate intake level(s)	• Comparison of different sources of carbohydrate without specifying amount of carbohydrate intake • Studies that do not attempt to control for energy intake of participants such that comparisons are made on an isocaloric basis. • Comparisons of available carbohydrate exposure should not be confounded by differences in participants' energy intake.
Outcomes	• Intermediate outcomes: o LDL cholesterol (LDL-C) o Total cholesterol (TC) o HDL cholesterol (HDL-C) o Non-HDL-C cholesterol o TC:HDL-C ratio o LDL-C:HDL-C ratio o Triglycerides o Blood pressure (systolic and/or diastolic) and hypertension • Final outcomes: o CVD (e.g., myocardial infarction, coronary heart disease, congestive heart failure, peripheral artery disease) o Stroke o CVD-related mortality	• Hypertensive disorders during pregnancy and/or lactation (e.g., chronic hypertension, gestational hypertension, preeclampsia-eclampsia, chronic hypertension with superimposed preeclampsia)
Timing	• At least 4 weeks	• Less than 4 weeks
Settings	• All except hospital and acute care	• Hospital and acute care
Study design	• Randomized controlled trials • Nonrandomized controlled trials, including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Nested case-control studies • Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	• In vitro studies, nonoriginal data (e.g., narrative reviews, scoping reviews, editorials, letters, or erratum), retrospective cohort studies, case series, qualitative studies, cost-benefit analysis, cross-sectional (i.e., nonlongitudinal) studies, survey
Publications	• Studies published in English only • Studies published in peer-reviewed journals • Studies published at and after the year 2000	• Non-English language studies

Abbreviations: CVD = cardiovascular disease; GI = gastrointestinal; HDL-C = high-density lipoprotein cholesterol; KQ = key question; LDL-C = low-density lipoprotein cholesterol; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial; TC = total cholesterol; U.S. = United States

2.3.2.2 Systematic Review of the Effect of Dietary Digestible Carbohydrate Intake on Risk of Type 2 Diabetes, Growth, Size, and Body Composition

The eligible studies for the KQ had to meet all of the following criteria: (1) general population over 2 years old, (2) reported total dietary digestible carbohydrate intake and isolated effect or association of carbohydrate intake from the effects of other macronutrients (e.g., adjustments of other macronutrients), (3) compared with different total dietary digestible carbohydrate intake level(s), (4) reported outcomes of interest (T2D, gestational diabetes, growth, size, body composition, and surrogate markers for prediabetes or abnormal glycemia); (5) followed participants at least 12 weeks, (6) were RCTs, nonrandomized controlled trials, prospective cohort studies, nested case-control studies; (7) were published in English as peer reviewed full text publications; and (8) were published after the year 2000 to focus on studies that were not included in the 2005 DRI for carbohydrate. We excluded studies with infants and children under 2 years old, participants who had diseases/health-related conditions that can impact carbohydrate absorption or metabolism, including cancer and malabsorption syndromes; participants who were already diagnosed with the endpoint outcomes of interest (i.e., type 1 or 2 diabetes); participants who intended to reduce weight or receive treatments for being overweight or having obesity through energy restriction or hypocaloric diets for the purposes of treating additional or other medical conditions, participants who were determined to be undernourished, underweight, stunted, or wasted; or participants who are pre-bariatric or post-bariatric surgery. We also excluded studies that did not describe the entire macronutrient distribution of the diet, assessed digestible carbohydrate intake via infusions (rather than the GI tract), evaluated only the quality or individual sources of carbohydrates, or included food products or dietary supplements not widely available in the U.S. Studies about hypertensive disorders during pregnancy and/or lactation were not evaluated. The detailed inclusion and exclusion criteria for the KQs are listed in Table 2.

2. Methods

Table 2. Inclusion and exclusion criteria by population, intervention, comparator, outcome, timing, setting/study design (PICOTS) for systematic review of type 2 diabetes, growth, size, and body composition

PICOTS Elements	Inclusion Criteria	Exclusion Criteria

Population	• General population, including participants who are determined to be overweight/obese, women who are pregnant or lactating
	• Age of participants
	  ○ Between 2 and 9 years (before puberty)
	  ○ Between 9 and 17 years
	  ○ 18 years and older
		• Studies that enroll participants with diseases/health-related conditions that impact carbohydrate absorption or metabolism including cancer and malabsorption syndromes
		• Studies that exclusively enroll participants hospitalized with an illness or injury
		• Studies that exclusively enroll participants with type 1 or 2 diabetes (i.e., studies that aim to treat participants who have already been diagnosed with the endpoint outcomes of interest)
		• Studies designed to induce weight loss or treat patients who are determined to be overweight and obese through energy restriction or hypocaloric diets for the purposes of treating additional or other medical conditions
		• Studies that exclusively enroll participants who are determined to be undernourished, underweight, stunted, or wasted
		• Studies that enroll participants who are pre-bariatric or post-bariatric surgery
		• Exclude participants less than 2 years old

2. Methods

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Interventions	• Total dietary digestible carbohydrate intake from foods, beverages, and dietary supplements ○ Total dietary digestible carbohydrate intake defined as collective starch and sugar intake; carbohydrate intake not including dietary fiber) • A dietary pattern that quantifies the intake of total dietary digestible carbohydrates and allows the isolation of the effect of carbohydrate intake from the effect of the intake of other macronutrients	• Studies that do not specify the amount of total digestible carbohydrate intake (e.g., studies that only report type or source of digestible carbohydrate) • Studies that do not describe the entire macronutrient distribution of the diet (i.e., studies that do not report total digestible carbohydrate, total fat, and total protein contents of experimental or baseline diets) • Studies that only assess digestible carbohydrate intake via infusions (rather than the GI tract) • Studies that primarily measure postprandial responses, as opposed to longer term studies • Studies that examine food products or dietary supplements not widely available to U.S. consumers • Multi-component interventions that do not isolate the effect or association of digestible carbohydrate
Comparators	• Different total dietary digestible carbohydrate intake level(s)	• Comparison of different sources of carbohydrates without specifying the amount of carbohydrate intake • Studies that do not attempt to control for the energy intake of participants such that comparisons are made on an isocaloric basis. • Comparisons of available carbohydrate exposure should not be confounded by differences in participants' energy intake.

Outcomes	• Incidence of T2D
	• Incidence of gestational diabetes
	• Surrogate markers suggesting prediabetes or abnormal glycemia
	  ○ HbA_{1C} level
	  ○ Glucose tolerance/insulin resistance/insulin sensitivity
	• Growth, size, and body composition
	  ○ Body weight
	  ○ BMI
	  ○ Body circumference
	  ○ Body composition and distribution
	  ○ Classifications of underweight, healthy weight, overweight, and obesity
		• Type 1 diabetes

PICOTS Elements	Inclusion Criteria	Exclusion Criteria

Timing	• T2D
	  ○ Minimum intervention length of 12 weeks
	• Effect on growth, size, and body composition
	  ○ Minimum intervention length of 12 weeks
		• Any intervention length <12 weeks

Settings	• All except hospital and acute care	• Hospital and acute care
Study design	• Randomized controlled trials • Nonrandomized controlled trials, including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Nested case-control studies • Relevant systematic reviews, or meta-analyses (used for identifying additional studies)	• In vitro studies, nonoriginal data (e.g., narrative reviews, scoping reviews, editorials, letters, or erratum), retrospective cohort studies, case series, qualitative studies, cost-benefit analysis, cross-sectional (i.e., nonlongitudinal) studies, survey
Publications	• Studies published in English only • Studies published in peer-reviewed journals • Studies published at and after the year 2000	• Non-English language studies

Abbreviations: BMI = body mass index; HbA_{1c} = hemoglobin A_{1C}; GI = gastrointestinal; KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and settings; RCT = randomized controlled trial; T2D = type 2 diabetes; U.S. = United States

2.3.2.3 Study Selection

Pairs of independent reviewers screened the titles and abstracts for all citations using prespecified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, again working in pairs, screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus. When consensus could not be reached, a third reviewer resolved the difference. When studies did not explicitly identify that carbohydrates were digestible, we made a determination based on discussions with content experts, review of reported percentages of total energy intake, and identification of whether fiber was a covariate in the statistical models.

2.3.3 Data Extraction

We developed a standardized data extraction form to extract study characteristics (e.g., author, year, study design, inclusion and exclusion criteria, participants characteristics, macronutrient distribution of the diet, exposure/intervention, comparisons, outcomes, and related items for assessing study quality and applicability). The standardized form was tested by all study team members using 10 randomly selected studies.

The reviewers worked independently to extract study details. A second reviewer reviewed the data extraction and resolved conflicts. When the included studies did not report all necessary information (e.g., methods and results), we contacted authors directly. DistillerSR® was used to create data extraction forms and facilitate data extraction.

2.3.4. Risk of Bias Assessment

We evaluated the risk of bias of the included studies using the Risk Of Bias In Non-Randomized Studies - of Intervention (ROBINS-I) tool[41] to assess bias from confounding,

selection of participants, classification of interventions, deviations from intended intervention, missing data, outcome measurements, and selection of the reported results. In addition, we extracted funding source of the included studies. We identified two eligible RCTs [42, 43]; however, as we are interested in the association between digestible carbohydrate intake and outcomes, the RCTs were presented and analyzed similarly to the other prospective cohort studies. We did not use the Cochrane Collaboration's Risk of Bias 2 tool.[44] One reviewer independently rated risk of bias for all studies. A second reviewer reviewed the ratings and resolved conflicts.

2.3.5. Data Synthesis and Analyses

We qualitatively summarized key features/characteristics (e.g., study populations, study design, exposure/intervention, comparison, outcomes, and conclusions) of the included studies and present the findings in evidence tables for each systematic review. Table 3 lists the definitions of selected outcomes used in the report.

Table 3. Definition of outcomes

Outcome	Definition
Cardiovascular disease	Myocardial infarction, unstable angina, congestive heart failure, peripheral artery disease, or intermittent claudication
Stroke	Ischemic and hemorrhagic stroke or transient-ischemic attack
Cardiovascular disease-related mortality	Death from myocardial infarction, heart failure, or stroke
Coronary heart disease	Atherosclerosis of the native coronary arteries manifesting as myocardial infarction, stable angina, or unstable angina
Type 2 diabetes	Hemoglobin A_{1C} of greater than or equal to 6.5%, fasting plasma glucose greater than or equal to 126 mg/dl, 2-hour post oral glucose tolerance test reading of greater than or equal to 200 mg/dl, or random glucose of greater than or equal to 200 mg/dl with typical symptoms of hyperglycemia.

Abbreviations: mg/dl = milligrams per deciliter

To isolate the effect of carbohydrate intake from confounding (e.g., by other macronutrients, physical activities, age, race/ethnicity), we extracted the most adjusted values regardless of study design. We extracted relative risk (RR) and corresponding 95 percent confidence intervals (CIs) for binary outcomes. We converted odds ratio (OR) to RR[45] and used VanderWeele's optimal bias-ratio minimax function to convert hazard ratio (HR) to RR.[46] For continuous outcomes, we extracted mean difference and related confidence intervals.

Digestible carbohydrate intake was extracted and presented as grams per day and percent energy from carbohydrate intake per day as reported in the original studies without conversion. To facilitate meta-analysis, we converted percent energy to grams, and vice versa, when the study provided exact total energy intake (i.e., we did not assume 2000 kcal total energy intake per day). We multiplied the percentage of energy intake by the total energy intake (kcal per day) and divided by 4, and vice versa. For studies reporting a range of digestible carbohydrate intake levels (e.g., tertile, quartile, quintile), we used the mid-point of the range as the mean daily intake. If the range was open ended, we used the half range of the adjacent range to establish the average carbohydrate intake for the open-ended range.

In studies reporting results from multiple prospective cohort studies, we extracted data from individual cohorts and reported and analyzed these data separately. If a study had multiple publications (e.g., the European Prospective Investigation into Cancer and Nutrition study,[47] the Nurses' Health Study[48]) and reported the same outcomes, we included the one with the longest followup.

We conducted dose-response meta-analyses to quantify the association between digestible carbohydrate intake and outcomes of interest. Nonlinear dose-response trends were evaluated using a one-stage random-effects dose-response model with restricted cubic splines and three knots at 10%, 50%, and 90% of the distribution.[49, 50] The linear trend was evaluated using a one-stage weighted linear random-effects does-response model.[49] We assumed 0 covariance between outcomes within each study (i.e., independence of observed outcomes at different levels of digestible carbohydrate intake within a study). Total digestible carbohydrate intake at 300 grams per day or 50% of total energy intake was set as the reference. We selected 50% as the reference carbohydrate intake level because it is within the range of the recommended 45%-65% total energy intake from carbohydrates by the Dietary Guidelines for Americans 2020-2025[51] and is close to the median carbohydrate intake (50.8%) reported in the included studies. Fifty percent of total energy intake translates to 300 grams of carbohydrates per day when a healthy person gets 2,200 calories per day. The reference can be changed by using the relative risk from the new reference level. We did not conduct pairwise meta-analyses (e.g., the highest level vs. the lowest level) because the included studies reported heterogeneous ranges and categorizations of digestible carbohydrate intake (e.g., tertile, quartile, quintile, decile). Subgroup analyses were conducted based on sex (woman vs. man) and geographic locations (East Asia vs. Western Countries). We evaluated heterogeneity between studies using Cochran's Q test, in which $p<0.10$ suggested substantial heterogeneity.[52] All statistical analyses were conducted using Stata version 17.0 (StataCorp LLC, College Station, TX, USA).

2.3.6. Grading the Strength of Evidence for Major Comparisons and Outcomes

We graded the strength of evidence (SOE) for KQs following a global and narrative approach[53] that describes the trustworthiness of the evidence across the various exposure doses and implying our certainty about the dose-response curve. We incorporated domains from the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[39] We graded SOE for the critical effectiveness outcomes: CVD, coronary heart disease (CHD), CVD-related mortality, stroke, T2D, and body weight. These outcomes were chosen because they are either clinically important from a patient's perspective or highly relevant for stakeholders' decision making.

SOE derived from observational studies started as low.[39] SOE was rated down due to methodological limitations of the studies (i.e. risk of bias), imprecision (based on the size of the body of evidence, number of events, and confidence intervals), indirectness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs. surrogates), inconsistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity), or increased likelihood of reporting and publication bias. SOE could be increased if a dose-response gradient was credible, consistent, and reproduced across multiple studies.[54]

We lowered the SOE rating for the risk of bias when the majority of the studies in a particular comparison had high or unclear risk of bias. When the majority of studies were not at high risk of bias and estimates from high and low risk of bias studies were similar, we combined them and did not rate down the SOE.

Based on this assessment and the initial study design, we assigned SOE rating as high, moderate, low, or 'insufficient evidence to estimate an effect' (Table 4).

Table 4. Definition of strength of evidence ratings

SOE Rating	Definition
High	We are very confident that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable).
Moderate	We are moderately confident that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable).
Low	We have limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable).
Insufficient	We have no evidence, are unable to estimate an effect, or have no confidence in the estimate of effect.

Abbreviations: SOE = strength of evidence

We produced summary of evidence tables that provided for each outcome: data source, effect size, SOE rating, and rationale for judgments made on each domain of evidence rating.

2.3.7. Assessing Applicability

We followed the procedures outlined in the AHRQ Methods Guide to assess the applicability of the findings within and across studies.[39] Applicability for each outcome was summarized and presented qualitatively using the PICOTS framework and not a specific checklist or scale. The following factors that may affect applicability have been identified, including patient factors (e.g., age, race, ethnicity, socioeconomic status, geographic location), settings, and study design features (e.g., observational studies, RCTs). We used this information to evaluate the applicability of the evidence to real-world clinical practice in typical U.S. settings. We reported any limitations in applicability of individual studies in the evidence tables and limitations of applicability of the whole body of evidence in the summary of evidence tables.

2.3.8. Peer Review and Public Commentary

To be added in the final version of the report.

3. Results

3.1 Systematic Review of the Effect of Dietary Digestible Carbohydrate Intake on Risk of Cardiovascular Disease

3.1.1 Literature Searches and Evidence Base

The literature search identified 8,818 citations. We excluded 6,805 articles after abstract screening. One thousand nine hundred eight-four articles were excluded after full-text screening. The main reasons for exclusion were not meeting inclusion criteria by study population (n=442), intervention/exposure and comparison (n=1,270), outcomes (n=107), study design (n=165). Twenty-one original studies reported in 29 articles with a total of 1,277,621 participants met the inclusion criteria [47, 48, 55-81] The results of the literature search are displayed in the flow chart in Appendix B. The excluded studies with reasons for exclusion are included in Appendix C.

All 21 included studies were prospective cohort studies.[47, 48, 55-81] The median age of the participants was 51.7 years (range: 24.8–57.9 years); 59.90% were women. No eligible studies evaluated children. The median digestible carbohydrate intake was 50.8% of total energy intake (range: 33.4%–79.0% of total energy intake) for studies reporting the percentage of total energy intake and 252.7 grams per day of carbohydrates for studies reporting grams per day (range: 138.8–368.7 grams per day). The median protein intake was 16.2% total energy intake (range: 11.4%–18.8% total energy intake). The median fiber intake was 21.9 grams per day (range: 8.7–25.1 grams per day); and the median fat intake was 30.7% total energy intake (range: 15.0%–45.2% total energy intake). Six studies were conducted in Europe (Finland, the United Kingdom (U.K.), Sweden, Germany, Italy, France, Denmark, Spain, the Netherlands); eight in Asia (Japan, Korea, China, and Singapore), one in Australia, five in the United States, and one on multiple continents. The median followup was 10.7 years, ranging from 1–32 years. Appendix Table D listed study characteristics, including participants, macronutrient distribution, and inclusion/exclusion criteria.

Appendices E and F list dietary assessment methods and the risk of bias by each study. Although all included studies used regression models to evaluate isolated effect of carbohydrate intake from other macronutrients as a part of inclusion criteria, 73.3% of the studies were deemed inadequate, missing one or more macronutrients in confounding adjustment. Dietary assessments were often conducted multiple times over the study period, facilitated by validated food frequency questionnaires, though recall periods typically were longer than 7 days. Overall, 80.0% of the studies were rated with serious risk of bias, 16.7% moderate risk, and 3.3% critical risk.

Appendices G through J include the results from included studies (Appendix G), results from linear dose-response meta-analysis (Appendix H), predicted relative risk of incident based on nonlinear dose-response meta-analysis (Appendix I), and subgroup analyses (Appendix J). Appendix K includes figures displaying the nonlinear dose relationships. Appendix L includes the appendix references.

3.1.2 Key Question

KQ: What is the association between dietary digestible carbohydrate intake and the incidence of cardiovascular disease?

3.1.2.1. Key Question Key Points

- A majority of the included studies reported inadequate confounding adjustment and were deemed to have serious risk of bias.
- No eligible studies evaluated children aged <18 years.
- The association between digestible carbohydrate intake and cardiovascular outcomes was nonlinear and supported by low strength of evidence.
- When digestible carbohydrate intake was analyzed as the percentage of total energy intake, the risk of incident cardiovascular disease (CVD) significantly increased when intake exceeded 65% total energy intake, compared with the carbohydrate intake reference level of 50%. The lowest risk was with an intake of 50% total energy intake. The risk of incident coronary heart disease increased starting at 45% total energy intake.
- When digestible carbohydrate intake was analyzed as grams per day, the risk of incident cardiovascular diseases significantly increased when intake exceeded 300 grams per day, compared with the carbohydrate intake reference level of 300 grams per day. The lowest risk was with an intake of 250 grams per day. The risk of incident coronary heart disease increased starting at 250 grams per day.
- The risk of cardiovascular disease-related mortality was U shaped and might be lowest with an intake 250–300 grams per day.
- The risk of stroke was not significantly associated with carbohydrate intake and had a less defined dose-response relationship. The risk increased when exceeded 50% total energy intake.
- The nonlinear relationships were overall similar based on sex or geographic location but with variable intake ranges associated with the lowest risk.
- Higher carbohydrate intake may be associated with lower levels of high-density lipoprotein cholesterol (HDL-C) and higher levels of triglycerides.

3.1.2.2. Key Question Results: Cardiovascular Disease

Seventeen studies[47, 48, 55, 57, 58, 61-66, 69, 73, 75, 79-81] with 1,264,870 participants evaluated the association between digestible carbohydrate intake and incident CVD. The median age of the participants was 52.5 years (range: 24.8–57.9 years). In the studies that reported the percentage of energy intake of digestible carbohydrate, the range was from 33.4% to 79.0% total energy intake. In the studies that reported grams per day, the range was from 138.8 to 368.7 grams per day of carbohydrates.

Nine studies[55, 57, 61, 63, 73, 79-81] reported significant association between digestible carbohydrate intake and incident CVD (three suggested reduction in risk, and six suggested increased in risk).

3.1.2.2.1. Studies Showing Risk Reduction

The Japan Multi-Institutional Collaborative Cohort (J-MICC) study[55] included 34,893 men and 46,440 women aged between 35 years and 69 years from Japan. With a mean followup of 8.9 years, in men, higher carbohydrate intake was associated with reduced risk of CVD-related mortality (per 10% total energy increase: hazard ratio [HR]=0.62, 95% confidence interval [CI]: 0.46 to 0.83; compared 50% to <55% total energy intake with 45% to <50% total energy intake: HR=0.43, 95% CI: 0.25 to 0.75). The Atherosclerosis Risk in Communities Study (ARIC)[63] included 13,385 adult U.S. participants. The mean carbohydrate intake was 48.8% of total energy

intake (standard deviation [SD]: 9.4) and the median followup was 22.4 years. There was a significant association of carbohydrate intake and lower risk of incident atrial fibrillation (per 9.4% increase in total energy intake, HR=0.82, 95% CI: 0.72 to 0.94). Compared with the lowest carbohydrate intake (Quartile 1: <42.7% total energy intake), higher carbohydrate intake was associated with reduced risk of incident atrial fibrillation (Quartile 2: 42.7%-48.5% total energy intake, HR=0.79, 95% CI: 0.68 to 0.92; Quartile 3: 48.6%–54.7% total energy intake, HR=0.77, 95% CI: 0.64 to 0.93; Quartile 4: ≥54.8% total energy intake, HR=0.64, 95% CI: 0.49 to 0.84). The Australian Longitudinal Study on Women's Health (ALSWH)[80] evaluated 9,899 Australian women aged between the ages of 50–55 years at baseline. After a 15-year followup, total digestible carbohydrate intake was found to be associated with reduced risk of incident CVD. Compared with low carbohydrate intake (Quintile 1: <37.1% total energy intake), higher digestible carbohydrate intake was associated with significantly reduced risk of CVD (Quintile 3: 41-44.3% total energy intake, odds ratio [OR]=0.56, 95% CI: 0.35-0.91).

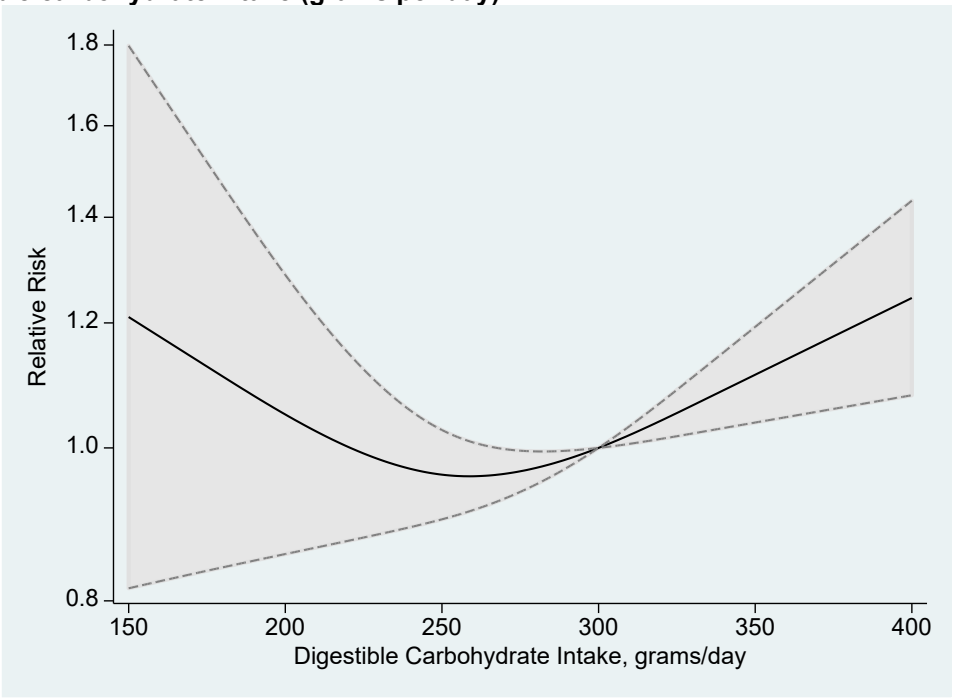
3.1.2.2.2. Studies Showing Risk Increase

Ho et al.[61] evaluated 195,658 adult participants from the U.K. Biobank Study. The mean carbohydrate intake was 49.6% of total energy intake (SD: 7.0) and mean followup was 9.7 years (range: 8.5–13.0 years). Compared with 50% total energy intake from carbohydrates, carbohydrate intake between 53% and 65% total energy intake was associated significantly increased risk of CVD. The Korean Association Resource (KARE) study[73] enrolled 9,608 Korean adults aged 40 years to 69 years. With a median followup of 9.6 years, the highest carbohydrate intake (Quartile 4: mean=78.7% total energy intake) was associated with significantly higher risk of incident CVD (HR=1.65, 95% CI: 1.04 to 2.62), compared with the lowest intake (mean=63.7% total energy intake). The Cohort Study on Risk Factors of Non-Communicable Diseases (CS-RFNCD)[79] included 4,840 adults aged above 25 years from Indonesia. Carbohydrate intake of ≥60% of total energy was associated with increased risk of incident CHD, compared with <60% of total energy intake (HR=2.79, 95% CI: 1.96 to 3.97). The Singapore Multi-Ethnic Cohort (MEC) [57] followed 12,408 Singaporean adults aged between 21 years to 65 years for a mean of 10.1 years. Compared with the lowest digestible carbohydrate intake (Quartile 1: median=46.6% total energy intake), higher carbohydrate intake was associated with significantly increased risk of major adverse cardiovascular events (Quartile 3: median=56.1% total energy intake, HR=1.34, 95% CI: 1.08 to 1.67; Quartile 4: median=61.5% total energy intake, HR=1.35, 95% CI: 1.07 to 1.71). The Hordaland Health Study (HUSK)[81] recruited 2,995 Norwegian adults between 46 years to 49 years at baseline. The mean followup was 10.8 years (SD: 1.3). Higher intake of carbohydrates (median=49% total energy intake) was associated with significantly increased risk of incident CHD (per 2% total energy intake increase, HR=1.12, 95% CI: 1.05 to 1.20). Compared with the lowest carbohydrate intake levels (Quartile 1: median=43% total energy intake), the highest carbohydrate intake was associated with significantly increased risk of CHD (Quartile 4: median=56% total energy intake, HR=2.10, 95% CI: 1.22 to 3.63). The European Prospective Investigation into Cancer and Nutrition (EPIC) study[47, 67, 68, 70, 78] included 338,325 adult participants. The median followup was 12.8 years, and the mean digestible carbohydrate intake was 231.80 grams per day. Digestible carbohydrate intake was associated with significantly increased risk of fatal and nonfatal CHD (per 50 grams per day increase, HR=1.11, 95% CI: 1.03-1.08).

3.1.2.2.3. Dose-Response Meta-Analysis

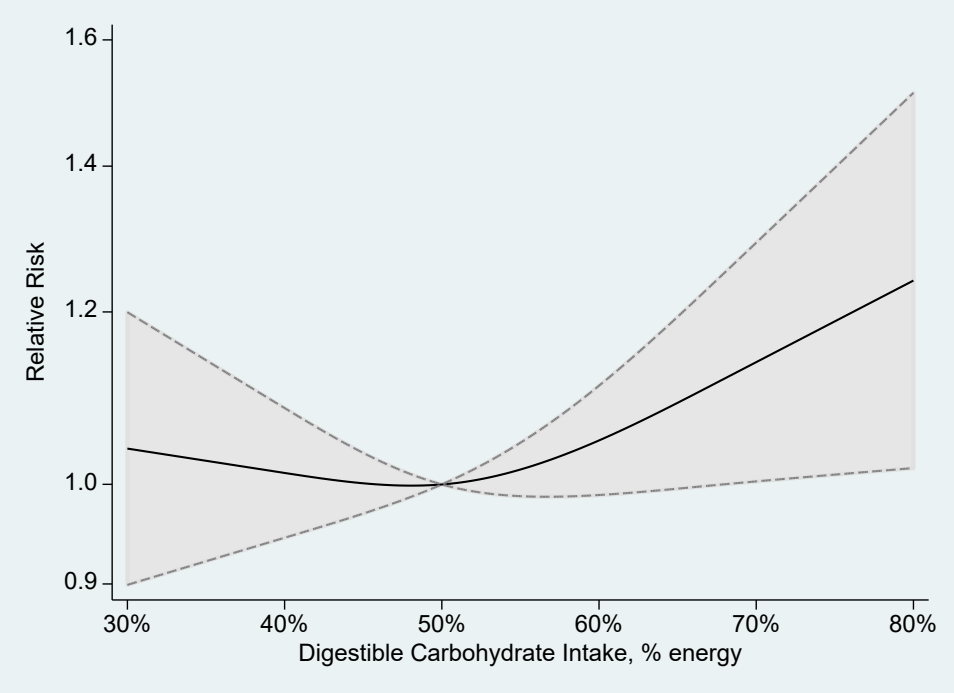
The linear dose-response meta-analysis showed no significant association between digestible carbohydrate intake and incident CVD (per 10-gram increase: relative risk [RR]=0.99; 95% CI: 0.97 to 1.02; per 10% total energy intake increase: RR=1.03; 95% CI: 0.96 to 1.09)(Appendix Table H.1). We observed significant nonlinear U-shaped dose response relationship (Figure 1, $P_{nonlinearity}$=0.03; and Figure 2, $P_{nonlinearity}$=0.03). Analyzing carbohydrate intake as a percentage of total energy intake showed a gradual decrease in the risk of incident CVD up to 50% total energy intake, followed by an increase at higher carbohydrate intake levels. Compared with a carbohydrate intake reference level of 50% total energy intake, a digestible carbohydrate intake exceeding 65% total energy intake was associated with a significantly increased risk of CVD. Similarly, analyzing carbohydrate intake in grams per day revealed a steady decline in CVD risk up to 250 grams per day, with an increased risk at higher carbohydrate intake levels. Compared with a carbohydrate intake reference level of 300 grams per day, exceeding 300 grams per day was associated with a significantly increased risk of CVD. Appendix Table I.1.1 and I.1.2 listed the predicted RR of incident CVD across a range of carbohydrate intake.

Figure 1. Nonlinear dose-response relationship between the incidence of cardiovascular disease and digestible carbohydrate intake (grams per day)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

Figure 2. Nonlinear dose-response relationship between the incidence of cardiovascular disease and digestible carbohydrate intake (% total energy intake)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

3.1.2.3. Key Question Results: Coronary Heart Disease

Nine studies[47, 48, 57, 58, 64-66, 79, 81] with 676,794 participants evaluated the risk of incident coronary heart disease (CHD). The median age of the participants was 48.0 years (range: 24.8–57.9 years). The range of digestible carbohydrate intake was from 33.4% to 79.0% for studies reporting a percentage of total energy intake and from 191.6 to 311.4 grams per day of carbohydrates for studies reporting grams per day.

Five studies[47, 57, 62, 79, 81]reported a significant association between carbohydrate intake and the risk of incident CHD, all suggesting some increase in risk.

The Singapore Multi-Ethnic Cohort (MEC) [57] followed 12,408 Singapore adults aged between 21 years to 65 years for a mean of 10.1 years. Compared with the lowest digestible carbohydrate intake (Quartile 1: median=46.6% total energy intake), higher carbohydrate intake was associated with significantly increased risk of CHD (Quartile 3: median=56.1% total energy intake, HR=1.54, 95% CI: 1.14 to 2.08; Quartile 4: median=61.5% total energy intake, HR=1.73, 95% CI: 1.26 to 2.38).

The Hordaland Health Study (HUSK)[81] recruited 2,995 Norwegian adults between 46 years to 49 years at baseline. The mean followup was 10.8 years (SD: 1.3). Higher intake of carbohydrates (median=49% total energy intake) was associated with significantly increased risk of incident CHD (per 2% total energy intake increase, HR=1.12, 95% CI: 1.05 to 1.20). Compared with the lowest carbohydrate intake (Quartile 1: median=43% total energy intake), the highest carbohydrate intake was associated with significantly increased risk of CHD (Quartile 4: median=56% total energy intake, HR=2.10% CI: 1.22 to 3.63).

The Cohort Study on Risk Factors of Non-Communicable Diseases (CS-RFNCD)[79] included 4,840 adults aged older than 25 years from Indonesia. A carbohydrate intake of ≥60% of total

energy was associated with increased risk of incident CHD compared with <60% of total energy (HR=2.79, 95% CI: 1.96 to 3.97).

The European Prospective Investigation into Cancer and Nutrition (EPIC) study[47, 67, 68, 70, 78] included 338,325 adult participants. The median followup was 12.8 years and mean digestible carbohydrate intake was 231.80 grams per day. Digestible carbohydrate intake was associated with significantly increased risk of fatal and nonfatal coronary heart disease (per 50-gram increase, HR=1.11, 95% CI: 1.03 to 1.08). However, compared with the lowest carbohydrate (≤202.0 grams per day), higher carbohydrate intake levels were not associated with coronary heart disease.

The National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged (NIPPON DATA) [62]included 8,925 Japanese participants aged 30 years to 79 years. In women, compared with the lowest digestible carbohydrate intake (Quartile 1: median=49.8% total energy intake), higher carbohydrate intake was associated with significantly higher risk of CHD-related mortality (Quartile 2: median=56.1% total energy intake; HR=3.11, 95% CI: 1.03-9.43; Quartile 3: median=60.3% total energy intake; HR=3.03, 95% CI: 1.06 to 10.03). No significant association was reported in men.

3.1.2.3.1. Dose-Response Meta-Analysis

The linear dose-response meta-analysis showed significant association between the risk of incident CHD and digestible carbohydrate intake as percent of total energy intake (per 10% total energy intake increase: RR=1.17; 95% CI: 1.02 to 1.34, Appendix Table H.1). The nonlinear dose-response relationship is presented in Figure 3 ($P_{nonlinearity}$=0.13) and Figure 4 ($P_{nonlinearity}$=0.01). Analyzing carbohydrate intake as a percentage of total energy intake showed a relatively flat risk of incident CHD up to 45%. However, the risk rose sharply when carbohydrate intake exceeded 45% of total energy intake. Compared with a carbohydrate intake reference level of 50%, exceeding 50% total energy intake with carbohydrate intake was associated with a significantly increased CHD risk. Similarly, analyzing carbohydrate intake in grams per day revealed a flat risk up to 250 grams per day of carbohydrates, followed by a sharp rise in risk at higher carbohydrate intake levels (Appendix Table I.1.3 and I.1.4).

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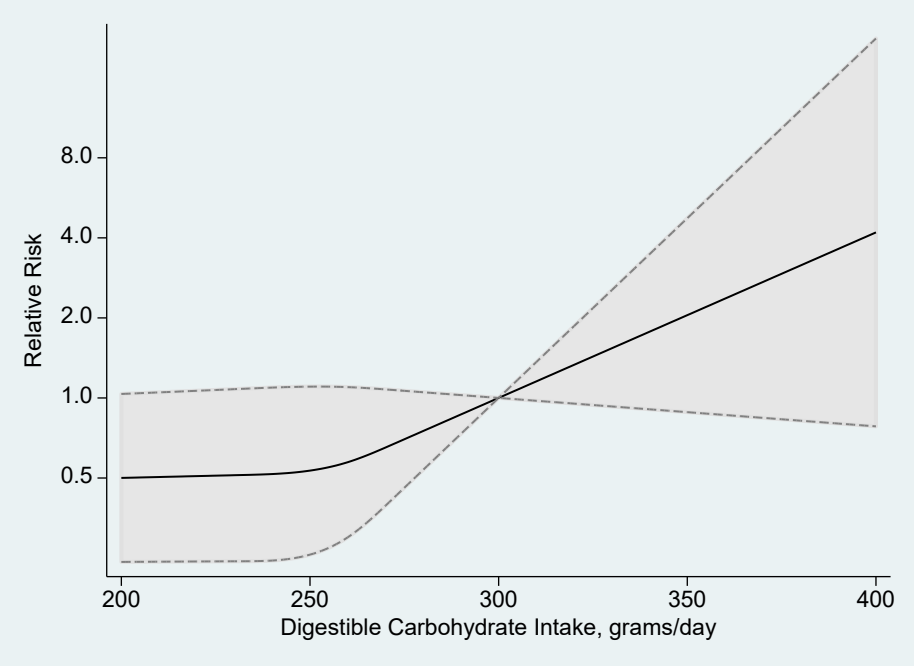
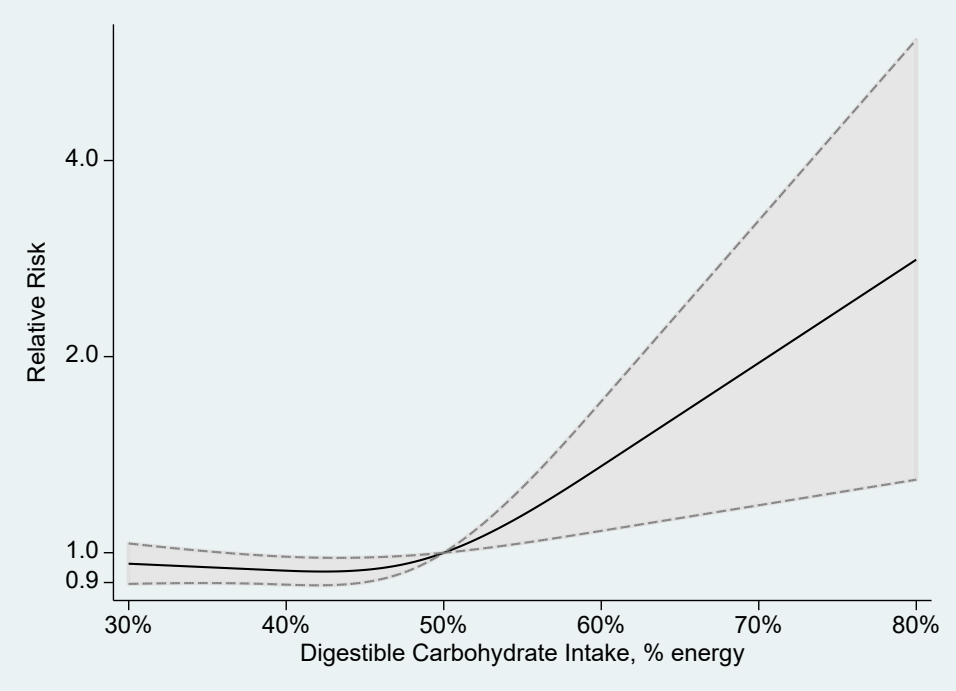
Figure 3. Nonlinear dose-response relationship between the incidence of coronary heart disease and digestible carbohydrate intake (grams per day)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

Figure 4. Nonlinear dose-response relationship between the incidence of coronary heart disease and digestible carbohydrate intake (% total energy intake)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

3.1.2.4. Key Question Results Cardiovascular Disease-Related Mortality

Five studies[55, 62, 64, 69, 75]with 330,774 participants reported CVD-related mortality. The median age of the participants was 50.3 years (range: 48.6–54.7 years). The range of digestible carbohydrate intake was from 40.5% to 77.2% for studies reporting the percentage of total energy intake and from 138.8 to 368.7 grams per day of carbohydrates for studies reporting grams per day.

Only one study[55] reported a significantly negative association between carbohydrate intake and CVD-related mortality. The Japan Multi-Institutional Collaborative Cohort (J-MICC) study[55] included 34,893 men and 46,440 women aged between 35 years and 69 years from Japan. With a mean followup of 8.9 years, in men, carbohydrate intake was associated with reduced risk of CVD-related mortality (per 10% total energy intake increase: HR=0.62, 95% CI: 0.46-0.83; compared 50% to <55% total energy intake with 45% to <50% total energy intake: HR=0.43, 95% CI: 0.25 to 0.75). There was no significant association in women.

3.1.2.4.1. Dose-Response Meta-Analysis

The linear dose-response meta-analysis showed nonsignificant association between carbohydrate intake and the risk of CVD-related mortality (per 10-gram increase: RR=1.00; 95% CI: 0.97 to 1.02; per 10% total energy intake increase: RR=1.00; 95% CI: 0.97 to 1.04). The U-shaped nonlinear dose-response relationship is presented in Figure 5 ($P_{nonlinearity}$=0.01) and Figure 6 ($P_{nonlinearity}$=0.50). Analyzing carbohydrate intake as a percentage of total energy intake showed a reduced risk of CVD-related mortality up to 55% total energy intake, after which the risk increased. Similarly, analyzing carbohydrate intake in grams per day showed a reduced risk up to 260 grams per day of carbohydrates, followed by an increased risk at higher carbohydrate intake levels. Compared with the carbohydrate intake reference level (300 grams per day), digestible carbohydrate intake below 215 grams per day was associated with significantly increased risk of CVD-related mortality (Appendix Table I.1.5and I.1.6).

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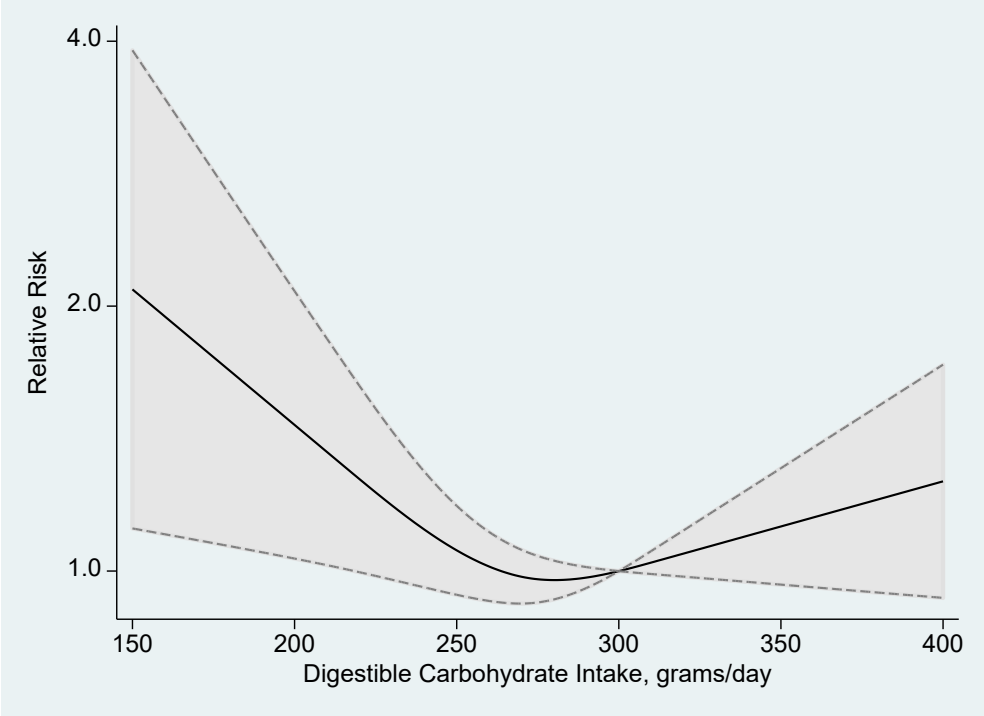
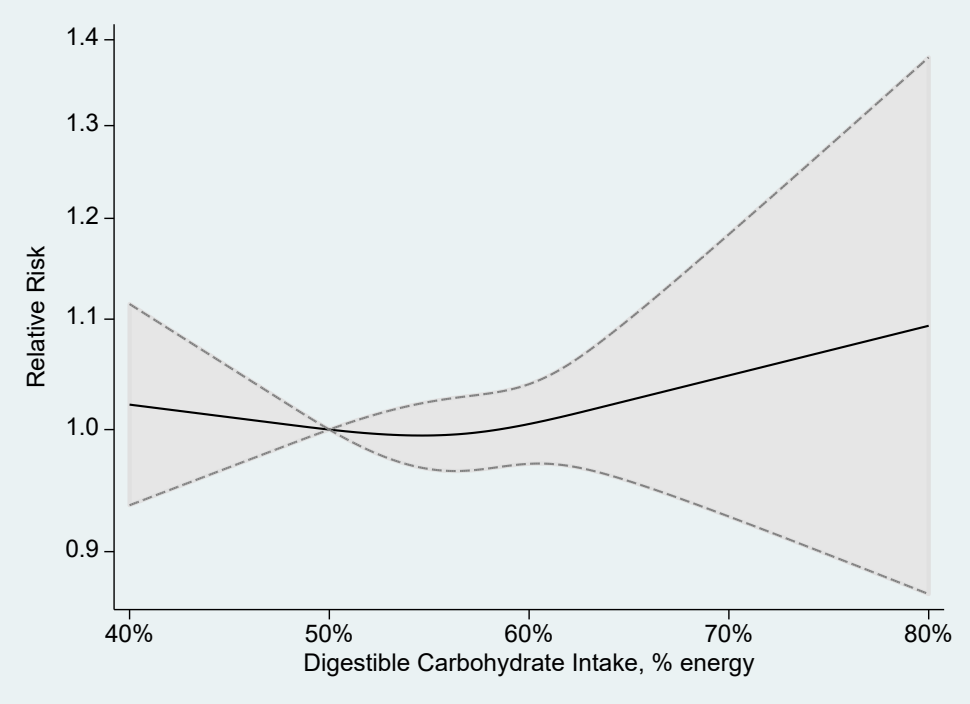
Figure 5. Nonlinear dose-response relationship between cardiovascular disease-related mortality and digestible carbohydrate intake (grams per day)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

Figure 6. Nonlinear dose-response relationship between cardiovascular disease-related mortality and digestible carbohydrate intake (% total energy intake)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

3.1.2.5. Key Question Results: Stroke

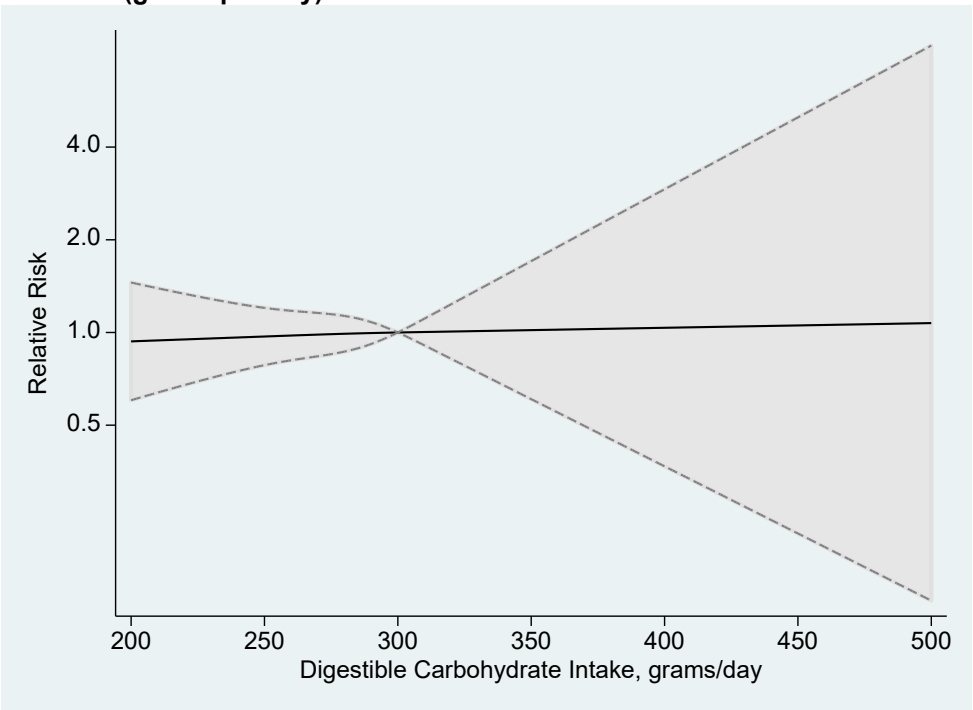
Nine studies[57, 58, 62, 64, 65, 67, 69, 72, 78] with 338,554 participants reported the association between digestible carbohydrate intake and the risk of incident stroke. The median age of the participants was 50.0 years (range: 24.8–57.9 years). The range of digestible carbohydrate intake was from 32.6% to 77.2% for studies reporting the percentage of total energy intake and 221.9–368.7 grams per day of carbohydrates for studies reporting grams per day.

All but one study reported no significant association between digestible carbohydrate intake and the risk of incident stroke.[78] Sieri et al., included 44,099 Italian participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) with a mean followup of 10.9 years and median digestible carbohydrate intake of 287 grams per day.[78] Digestible carbohydrate intake was associated with significantly increased risk of incident stroke (HR=1.49, 95% CI: 1.18-1.90). Compared with the lowest carbohydrate intake (Quintile 1: median=232 grams per day), only the highest carbohydrate intake was associated with significantly increased risk of stroke (Quintile 5: median=339 grams per day; HR=2.01, 95% CI: 1.04 to 3.86).

3.1.2.5.1. Dose-Response Meta-Analysis

The linear dose-response meta-analysis showed a nonsignificant relationship between carbohydrate intake and the risk of incident stroke (per 10-gram increase: RR=0.99; 95% CI: 0.95 to 1.04; per 10% total energy intake increase: RR=1.01; 95% CI: 0.95 to 1.07). Figures 7 and 8 reflect the nonlinear dose-response association ($P_{nonlinearity}$=1.00, $P_{nonlinearity}$=0.42, respectively). The risk of incident stroke was generally flat until 50% of total energy intake and then the risk gradually increased with higher carbohydrate intake (Appendix Table I.1.7 and I.1.8).

Figure 7. Nonlinear dose-response relationship between the incidence of stroke and digestible carbohydrate intake (grams per day)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

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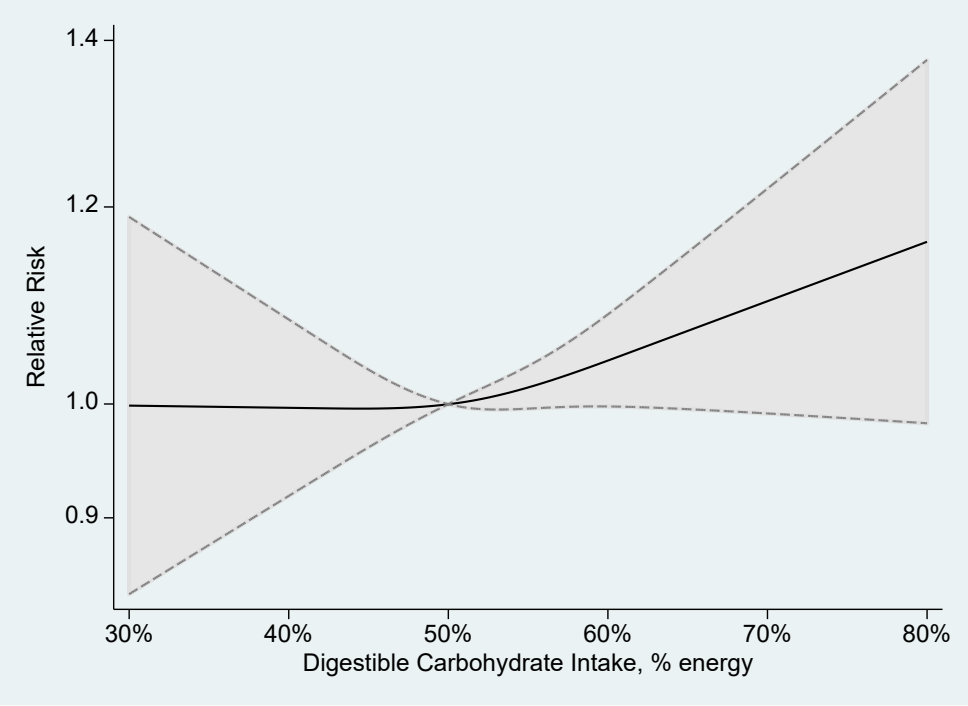
Figure 8. Nonlinear dose-response relationship between the incidence of stroke and digestible carbohydrate intake (% total energy intake)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

3.1.2.6. Key Question Results: Strength of Evidence for Cardiovascular Outcomes

Table 5 summarizes strength of evidence evaluation for cardiovascular outcomes.

Table 5. Strength of evidence of the association between digestible carbohydrate intake and cardiovascular outcomes

Outcome	Effect	SOE	Rationale
Incident cardiovascular disease	17 studies[47, 48, 55, 57, 58, 61-66, 69, 73, 75, 79-81] with 1,264,870 participants (median age of 52.5 years) • Nonsignificant association with carbohydrate intake (per 10-gram increase: RR=0.99; 95% CI: 0.97 to 1.02; per 10% E increase: RR=1.03; 95% CI: 0.96 to 1.09). • U-shaped nonlinear association. • Highest association was observed when intake exceeded 65% E. Lowest risk with intake 50% E. • Highest association was observed when intake exceeded 300 grams per day. Lowest risk with intake 250 grams per day.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Serious risk of bias.
Incident coronary heart disease	9 studies[47, 48, 57, 58, 64-66, 79, 81] with 676,794 participants (median age of 48.0 years) • Significant association with carbohydrate intake (per 10% E increase: RR=1.17; 95% CI: 1.02 to 1.34). • U-shaped nonlinear association. • Risk significantly increased starting at 250 grams per day • Risk significantly increased starting at 45% E.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Serious risk of bias.

3. Results

Outcome	Effect	SOE	Rationale
Cardiovascular disease-related mortality	5 studies[55, 62, 64, 69, 75] with 330,774 participants (median age of 50.3 years) • Nonsignificant associations with carbohydrate intake (per 10-gram increase: RR=1.00; 95% CI: 0.97 to 1.02; per 10% E increase: RR=1.00; 95% CI: 0.97 to 1.04). • U-shaped nonlinear association. • Significantly increased risk below 215 grams per day.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Wide confidence intervals or risk estimates across the majority of the intake range. • Serious risk of bias.
Incident stroke	9 studies[57, 58, 62, 64, 65, 67, 69, 72, 78] with 338,554 participants (median age of 50.0 years). • All but one study showed nonsignificant association. • Dose-response meta-analysis also showed nonsignificant associations. • Less defined nonlinear dose-response association with increase in risk at 50% E.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Wide confidence intervals or risk estimates across the majority of the intake range. • Serious risk of bias.

Abbreviations: %E=percentage of total energy intake; CI = confidence interval; RR = relative risk; SOE = strength of evidence

3.1.2.7. Key Question Results: Intermediate Outcomes

Five studies[58, 59, 71, 74, 80] with 51,990 participants reported intermediate outcomes, including hypertension, total cholesterol, triglycerides, HDL-C, low-density lipoprotein cholesterol (LDL-C), non-HDL-C, and TC-to-HDL-C ratio. The reported median range of digestible carbohydrate intake was from 35.2% to 71.1% of total energy intake.

Two studies[59, 80]with 22,076 participants evaluated incident hypertension. The China Health and Nutrition Survey[59] included 12,177 adult participants with a median followup of 6.1 years. A U-shaped association between total digestible carbohydrate intake and hypertension was observed with the lowest risk at 50% to 55% total energy intake from digestible carbohydrates. Compared with the lowest carbohydrate intake (Quintile 1: mean=41.3% total energy intake), risk of new-onset hypertension initially reduced (Quintile 2: mean=51.4% total energy intake, RR=0.77, 95% CI: 0.69 to 0.86) and then increased (Quintile 5: mean=71.1% total energy intake, RR=1.56, 95% CI: 1.38 to 1.75). The Australian Longitudinal Study on Women's Health (ALSWH)[80] evaluated 9,899 Australian women aged between 50–55 years at baseline. After a 15-year followup, total digestible carbohydrate intake was found to be associated with reduced risk of hypertension. Compared with the lowest carbohydrate intake (Quintile 1: <37.1% total energy intake), higher digestible carbohydrate intake was associated with significantly reduced risk of hypertension (Quintile 2: 37.1% to 41% total energy intake, OR=0.44, 95% CI: 0.32 to 0.59; Quintile 3: 41-44.3% total energy intake, OR=0.29, 95% CI: 0.20 to 0.40; Quintile 4: 44.3% to 48.1% total energy intake, OR=0.23, 95% CI: 0.15-0.34; Quintile 5: >48.1% total energy intake, OR=0.14, 95% CI: 0.09 to 0.24).

Two studies[71, 74] with 25,213 participants reported the association between digestible carbohydrate intake and HDL-C level. Kelly et al.[74] evaluated 24,639 participants from the U.K. Biobank Study with up to 3-year followup. Compared with the lowest carbohydrate intake (Quintile 1: mean=39.2% total energy intake/205.6 grams per day), higher carbohydrate intake levels were associated with significantly reduced HDL-C (mmol/L) from Quintile 2 (mean=46.04% total energy intake/241.8 grams per day; relative geometric mean=0.97, 95% CI: 0.96 to 0.97) to Quintile 5 (mean=59.11% total energy intake/284.79 grams per day; relative geometric mean=0.93, 95% CI: 0.92 to 0.93). The Seasonal Variation in Blood Cholesterol Levels Study (SEASONS)[71] enrolled 574 healthy adults aged between 20 years to 70 years from the United States. The mean digestible carbohydrate intake was 51% of total energy intake or 247 grams per day. With a 1-year followup, 5% increase of energy intake from carbohydrate intake was associated with a significant reduction of HDL-C levels (-1.86 mg/dl, p=0.03).

Two studies with 25,213 participants evaluated total cholesterol levels. [71, 74] Kelly et al.[74] evaluated 24,639 participants from the U.K. Biobank Study with a up to 3 years of followup. Compared with the lowest carbohydrate intake (Quintile 1: mean=39.2% total energy intake/205.6 grams per day), higher carbohydrate intake levels were associated with significantly reduced total cholesterol (mmol/L) from Quintile 2 (mean=46.04% total energy intake/241.8 grams per day; relative geometric mean=0.98, 95% CI: 0.98 to 0.99) to Quintile 5 (mean=59.11% total energy intake/284.79 grams per day; relative geometric mean=0.97, 95% CI: 0.96 to 0.97). The Seasonal Variation in Blood Cholesterol Levels Study (SEASONS)[71] enrolled 574 healthy adults aged between 20 years to 70 years from the United States. The mean digestible carbohydrate intake was 51% of total energy intake or 247 grams per day. With a 1-year followup, 5% increase of energy intake from carbohydrate intake was associated with a nonsignificant reduction of total cholesterol (-1.72 mg/dl, p=0.54).

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Three studies[58, 71, 74] with 29,914 participants evaluated LDL-C levels. Kelly et al.[74] evaluated 24,639 participants from the U.K. Biobank Study with a up to 3-year followup. Compared with the lowest carbohydrate intake (Quintile 1: mean=39.2% total energy intake/205.6 grams per day), higher carbohydrate intake levels were associated with significantly reduced LDL-C (mmol/L) from Quintile 2 (mean=46.04% total energy intake/241.8 grams per day; relative geometric mean=0.99, 95% CI: 0.98 to 0.99) to Quintile 5 (mean=59.11% total energy intake/284.79 grams per day; relative geometric mean=0.97, 95% CI: 0.97 to 0.98). The Seasonal Variation in Blood Cholesterol Levels Study (SEASONS)[71] enrolled 574 healthy adults aged between 20 to 70 years from the United States. The mean digestible carbohydrate intake was 51% of total energy intake or 247 grams per day. With a 1-year followup, 5% increase of energy intake from carbohydrate intake was associated with a nonsignificant reduction of total LDL-C (-0.84 mg/dl, p=0.75). The Coronary Artery Risk Development in Young Adults (CARDIA) cohort study[58] enrolled 4,701 U.S. adults aged 18–30 years at baseline. Over a period of 20 years, there was no significant association between LDL-C and digestible carbohydrate intake (p=0.26).

Two studies with 25,213 participants evaluated triglycerides levels. [56, 61, 71, 74] Kelly et al.[74] evaluated 24,639 participants from the U.K. Biobank Study with a up to 3-year followup. Compared with the lowest carbohydrate intake (Quintile 1: mean=39.2%/205.6 grams per day), higher carbohydrate intake levels were associated with significantly increased triglycerides (mmol/L) from Quintile 2 (mean=46.04% total energy intake/241.8 grams per day; relative geometric mean=1.04, 95% CI: 1.02 to 1.05) to Quintile 5 (mean=59.11% total energy intake/284.79 grams per day; relative geometric mean=1.11, 95% CI: 1.09 to 1.12). The Seasonal Variation in Blood Cholesterol Levels Study (SEASONS)[71] enrolled 574 healthy adults aged between 20 to 70 years from the United States. The mean digestible carbohydrate intake was 51% of total energy intake or 247 grams per day. With a 1-year followup, 5% increase of energy intake from carbohydrate intake was associated with a nonsignificant increase of triglycerides (1.04 mg/dl, p=0.36).

Two studies with 25,213 participants evaluated TC-to-HDL-C ratio.[56, 61, 71, 74] Kelly et al.[74] evaluated 24,639 participants from the U.K. Biobank Study with a up to 3-year followup. Compared with the lowest carbohydrate intake (Quintile 1: mean=39.2% total energy intake/205.6 grams per day), higher carbohydrate intake levels were associated with significantly increased TC-to-HDL-C ratio from Quintile 2 (mean=46.04% total energy intake/241.8 grams per day; relative geometric mean=1.02, 95% CI: 1.01 to 1.02) to Quintile 5 (mean=59.11% total energy intake/284.79 grams per day; relative geometric mean=1.04, 95% CI: 1.03 to 1.05). The Seasonal Variation in Blood Cholesterol Levels Study (SEASONS)[71] enrolled 574 healthy adults aged between 20 to 70 years from the United States. The mean digestible carbohydrate intake was 51% of total energy intake or 247 grams per day. With a 1-year followup, 5% increase of energy intake from carbohydrate intake was associated with a significant increase of TC-to-HDL-C ratio (0.20, p=0.03).

Kelly et al.[74] evaluated 24,639 participants from the U.K. Biobank Study with a up to 3-year followup. Compared with the lowest carbohydrate intake (Quintile 1: mean=39.2% total energy intake/205.6 grams per day), higher carbohydrate intake was associated with significantly increased TG-to-HDL-C ratio from Quintile 2 (mean=46.04% total energy intake/241.8 grams per day; relative geometric mean=1.07, 95% CI: 1.05 to 1.09) to Quintile 5 (mean=59.11% total energy intake/284.79 grams per day; relative geometric mean=1.19, 95% CI: 1.17 to 1.21).

3. Results

The Coronary Artery Risk Development in Young Adults (CARDIA) cohort study[58] enrolled 4,701 U.S. adults aged 18–30 years at baseline. Over a period of 20 years, there was no significant association between non-HDL-C and digestible carbohydrate intake (p=0.86).

3.1.2.8. Subgroup Analyses: Cardiovascular Disease

3.1.2.8.1 Sex

3.1.2.8.1.1. Women

Twelve studies[48, 55-57, 62, 65, 67-70, 72, 75-77, 80] reported findings about women separately. Four studies (33.3%) a reported significant association between digestible carbohydrate intake and incident CVD risk.[48, 57, 62, 68, 72, 77] The National Integrated Project for Prospective Observation of Non-Communicable Disease and its Trends in the Aged (NIPPON DATA)[62] included 5,009 Japanese women aged 30–79 years (mean=50.2 years, SD: 12.7) and with a followup of 24 years. Higher carbohydrate intake was associated with increased risk of CHD-related mortality (Quartile 2: mean=56.1% total energy intake; HR=3.11, 95% CI:1.03 to 9.43; Quartile 3: mean 60.3% total energy intake, HR=3.03, 95% CI:1.06 to 10.03), compared with the lowest carbohydrate intake (Quartile 1: mean=49.8% total energy intake). There was no significant association on CVD-related mortality or death from stroke.

The Singapore Multi-Ethnic Cohort (MEC) [57] followed 7,077 Singaporean adult women. Compared with the lowest digestible carbohydrate intake, higher carbohydrate intake was associated with significantly increased risk of major adverse cardiovascular events (Quartile 3: HR=1.60, 95% CI: 1.10 to 2.30; Quartile 4: HR=1.63, 95% CI: 1.10 to 2.40).

The Nurses' Health Study (NHS)[48, 72, 77] included 78,779 women aged 30–55 years at baseline and with a followup of 18 years. There was no significant association between carbohydrate intake and total stroke (ischemic stroke and hemorrhagic stroke) or ischemic stroke. However, higher carbohydrate intake was associated with significant increased risk of hemorrhagic stroke (Quintile 2: median=39.6% total energy intake: RR=1.60, 95% CI: 1.05 to 2.43; Quintile 3: median=43.8% total energy intake, RR=1.77, 95% CI: 1.09 to 2.88; Quintile 4: median=47.6% total energy intake, RR=1.99, 95% CI: 1.16 to 3.43; Quintile 5: median=52.9% total energy intake, RR=2.05, 95% CI: 1.10 to 3.83). Among women with a of body mass index (BMI) $\geq$ 25 kg/m^2, similar significant associations were found on increased risk of total stroke and hemorrhagic stroke.

The EPICOR study[68] is the Italian cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which included 30,495 adult women aged between 35–74 years. Compared with the lowest carbohydrate intake (Quartile 1: median=233.9 grams per day), women in the higher carbohydrate intake quartile had significantly higher risk of incident CHD (Quartile 2: median=273.7 grams per day; RR=1.79, 95% CI: 1.05 to 3.05; Quartile 3: median=299.3 grams per day; RR=1.89, 95% CI: 1.11 to 3.22; Quartile 4: median=337.8 grams per day; RR=2.00, 95% CI: 1.16 to 3.43).

3.1.2.8.1.2. Men

Nine studies[48, 55-57, 62, 65-68, 76] reported results exclusively in men. Only two studies (25.0%) found a statistically significant association between carbohydrate intake and the risk of incident CVD.[55, 67]

The Japan Multi-Institutional Collaborative Cohort (J-MICC) study[55] included 34,893 Japanese men between 35–69 years. With a mean followup of 8.9 years, in men, carbohydrate

intake was associated with reduced risk of CVD-related mortality (per 10% total energy intake increase: HR=0.62, 95% CI: 0.46 to 0.83; compared 50% to <55% total energy intake with 45% to <50% total energy intake: HR=0.43, 95% CI: 0.25 to 0.75).

The EPIC-MORGEN cohort[67] consisted of 8,855 men from the Netherlands with a mean followup of 11.9 years. In men, higher carbohydrate intake was significantly associated with increased risk of CHD (per 30.1 grams per day increase, HR=1.20, 95% CI: 1.02 to 1.43). The study did not find significant association on stroke.

3.1.2.8.1.3. Dose-Response Meta-analyses

We found no significant linear dose-response association between carbohydrate intake and incident CVD either in men or women (Appendix Table J.3). Appendix Figure K.3.1 and K.3.2 showed similar nonlinear U-shaped dose-response relationship in women ($P_{nonlinearity}<0.001$) and men ($P_{nonlinearity}=0.32$), with the lowest risk at 225 grams per day for women and 280 grams per day for men.

3.1.2.8.2. Geographic Locations

3.1.2.8.2.1. Western Countries

Ten studies[47, 48, 58, 61, 63, 65, 66, 75, 80, 81] conducted in Western countries (i.e., Australia, the United States, and countries in Europe) included 820,471 participants and reported the association between digestible carbohydrate intake and incident CVD. The median digestible carbohydrate intake ranged from 33.4% to 61.2% of total energy intake or 148.1 to 305.2 grams per day.

Two studies reported significantly reduced risk of incident CVD.[63, 80] The Atherosclerosis Risk in Communities Study (ARIC)[63] found higher carbohydrate intake was associated with reduced risk of incident atrial fibrillation; while the Australian Longitudinal Study on Women's Health (ALSWH)[80] found reduced risk of incident CVD associated with higher carbohydrate intake.

Three studies reported significantly increased CVD risk.[47, 56, 61, 67, 68, 70, 74, 78, 81] The Hordaland Health Study (HUSK)[81] reported that higher intake of carbohydrates was associated with significantly increased risk of incident CHD. The European Prospective Investigation into Cancer and Nutrition (EPIC) study[47, 67, 68, 70, 78] reported that digestible carbohydrate intake was associated with significantly increased risk of fatal and nonfatal CHD. Data from the U.K. Biobank Study[56, 61, 74] showed carbohydrate intake between 53% and 65% of total energy intake was associated significantly increased risk of CVD compared with 50% total energy intake from carbohydrate.

3.1.2.8.2.2. East Asian Countries

Six studies[55, 57, 62, 69, 73, 79] conducted in East Asia (Korea, Japan, China, and Singapore) reported the association between digestible carbohydrate intake and incident CVD. The median digestible carbohydrate intake ranged from 42.5% to 79.0% of total energy intake or 138.8 to 368.7 grams per day.

Three studies, the Korean Association Resource (KARE) study,[73] the Cohort Study on Risk Factors of Non-Communicable Diseases (CS-RFNCD),[79] and the Singapore Multi-Ethnic Cohort (MEC)[57] reported significantly increased risk of CVD was associated with higher carbohydrate intake, while the Japan Multi-Institutional Collaborative Cohort (J-MICC) study[55] found reduced risk of CVD-related mortality associated with increased carbohydrate intake in adult men.

3.1.2.8.2.3. Dose-Response Meta-analysis

In studies conducted in Western Countries, we found no significant linear dose-response association between carbohydrate intake and incident CVD (Appendix Table J.1). However, Appendix Figures K.1.2, and K.1.4 showed significant nonlinear dose-response association ($P_{nonlinearity}$=0.04, $P_{nonlinearity}$=0.05, respectively)

In East Asian studies, higher carbohydrate intake was significantly associated with significantly increased incident CVD (per 10% total energy intake increase, RR=1.11, 95% CI: 1.00 to 1.23, Appendix Table J.1). The significant nonlinear dose-response associations showed U-shaped relationships (Appendix Figure K.1.1, $P_{nonlinearity}$=0.03; Appendix Figure K.1.3, $P_{nonlinearity}$=0.04). Analyzing carbohydrate intake as a percentage of total energy intake showed a reduced risk of incident CVD up to 55% total energy intake, after which the risk increased with higher carbohydrate intake levels. Similarly, analyzing carbohydrate intake in grams per day showed a reduced risk up to 280 grams per day, followed by an increased risk at higher carbohydrate intake levels.

Although the nonlinear dose-response relationship showed a similar U-shaped relationship in studies conducted in Western Countries and in East Asia, studies conducted in Western Countries suggested lower carbohydrate intake levels at the lowest CVD risk (225 grams per day: RR=0.91, 95% CI: 0.87 to 0.96), compared with those in East Asia (285 grams per day: RR=1.00, 95% CI: 0.97 to 1.04).

3.2. Systematic Review of the Effect of Dietary Digestible Carbohydrate Intake on Risk of Type 2 Diabetes, Growth, Size, and Body Composition

3.2.1. Literature Searches and Evidence Base

The literature search identified 12,082 citations. We excluded 10,069 articles after abstract screening. One thousand nine hundred ninety-one articles were excluded after full-text screening. The main reasons for exclusion were not meeting inclusion criteria by the study population (n=442), intervention/exposure and comparison (n=1,269), outcomes (n=111), study design (n=169). The excluded studies with exclusion reasons are listed in Appendix C. Seventeen original studies reported in 22 articles with a total of 463,228 participants met our inclusion criteria and were included in the analyses. The results of the literature search are displayed in the flow chart in Appendix B.

Of the 17 included studies[42, 43, 80, 82-100], there were 15 prospective cohort studies. Only two randomized controlled trials (RCTs)[42, 43] were identified; however, as we are interested in the association between digestible carbohydrate intake and outcomes, the RCTs were presented and analyzed similarly to the other prospective cohort studies without reporting the difference between the original intervention and the control. The median age of the participants was 49.3 years (range: 31.1–63.3 years); 75.63% were women. We found no eligible studies in children. The median digestible carbohydrate intake was 49.3% for studies reporting the percentage of total energy intake (range: 28.3%–80.6% of total energy intake) and 294.9 grams per day of carbohydrates for studies reporting grams per day (range: 104.4–432.7 grams per day); the median protein intake was 17.0% of total energy intake (range: 10.7%–19.3% of total energy intake); the median fat intake was 33.7% of total energy intake (range: 17.2%–44.8% of total energy intake); and the median fiber intake was 19.8 grams per day (range: 9.6–42.2 grams per

day). Six studies were conducted in Europe (Finland, the United Kingdom, Sweden, Germany, Italy, France, Denmark, Spain, the Netherlands), five in East Asia (Japan, Korean, China), one in the Middle East (Iran), two in Australia, and three in the United States. The median followup was 10.0 years, ranging from 16 weeks to 20 years. Appendix Table D listed study characteristics, including participants, macronutrient distribution, and inclusion/exclusion criteria.

Appendices E and F list dietary assessment methods and the risk of bias by each study. Appendices G through J include the results from included studies (Appendix G), results from linear dose-response meta-analysis (Appendix H), predicted relative risk of incident based on nonlinear dose-response meta-analysis (Appendix I), and subgroup analyses (Appendix J). Appendix K includes figures displaying the nonlinear dose relationships. Although all included studies used regression models to evaluate isolated effect of carbohydrate intake from other macronutrients as a part of inclusion criteria, 79.2% of the studies were deemed inadequate in the confounding adjustment because they were missing one or more macronutrients. Dietary assessments were often conducted multiple times over the study period, facilitated by validated food frequency questionnaires, although recall periods typically were longer than 7 days. Overall, 91.7% of the studies were rated with serious risk of bias, and 8.3% had moderate risk. None of the studies were rated as low or critical risk of bias.

3.2.2. Key Question

KQ: What is the association between dietary digestible carbohydrate intake and the incidence of type 2 diabetes (T2D) and effect on growth, size, and body composition (i.e., obesity, overweight, body weight and composition)?

3.2.2.1. Key Question Key Points

- A majority of the included studies reported inadequate confounding adjustment and were deemed to have serious risk of bias.
- No eligible studies evaluated children aged <18 years.
- The association between carbohydrate intake and incident T2D was nonlinear and supported by low strength of evidence.
- When digestible carbohydrate intake was analyzed as the percentage of total energy intake, the risk of incident T2D gradually decreased from lowest intake until 45% total energy intake, remained relatively flat between 45% and 55% total energy intake and then increased gradually from 55% total energy intake.
- When digestible carbohydrate intake was analyzed as grams per day, the risk of incident T2D gradually decreased from lowest intake until 270 grams per day, remained relatively flat between 270 and 350 grams per day, and then increased gradually from 350 grams per day.
- The evidence was insufficient to determine an association between carbohydrate intake and weight or body composition.
- The nonlinear associations were overall similar based on sex but with variable intake range associated with the lowest risk.
- Very few studies evaluated surrogate outcomes.

3.2.2.2. Key Question Results: Incident Type 2 Diabetes and Gestational Diabetes

No study evaluated incident gestational diabetes. Eleven studies from 18 publications[43, 80, 82, 85-87, 89-100] with 452,586 participants evaluated incident T2D. The median age of the participants was 52.5 years (range: 36.1–58.0 years). The reported range of digestible carbohydrate intake was from 149.8 to 432.7 grams per day of carbohydrates for studies reporting grams per day or from 28.3% to 80.1% for studies reporting the percentage of total energy intake.

Most of the included studies reported no significant association between digestible carbohydrate intake and the risk of incident T2D. Only one study reported a significantly increased risk of T2D with increased carbohydrate intake,[96] and two studies reported reduced risk.[43, 80] The Shanghai Women's Health Study[96] included 74,942 Chinese women aged between 40 years and 70 years at baseline. At the end of followup (median=5 years), the highest digestible carbohydrate intake (Quintile 5: mean=337.6 grams per day) was associated with significantly increased risk of T2D, compared with the lowest digestible carbohydrate intake (Quintile 1: mean=263.5 grams per day) (RR=1.28, 95% CI: 1.09 to 1.50).

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)[43] was originally a double-blinded RCT that compared alpha-tocopherol, beta-carotene, or both on the incidence of lung cancer and other types of cancer. A total of 25,943 Finnish male smokers aged between 50–69 years at baseline were recruited and followed for 12 years. Compared with the lowest carbohydrate intake (Quintile 1: median=33.4% total energy intake), higher carbohydrate intake was associated with significantly reduced risk of T2D (Quintile 2: median=37.5% total energy intake, RR=0.77, 95% CI: 0.65 to 0.92; Quintile 3: median=40.4% total energy intake, RR=0.81, 95% CI: 0.68 to 0.97; Quintile 4: median=43.3% total energy intake, RR=0.81, 95% CI: 0.68 to 0.98; Quintile 5: median=47.4% total energy intake, RR=0.78, 95% CI: 0.95 to 0.99).

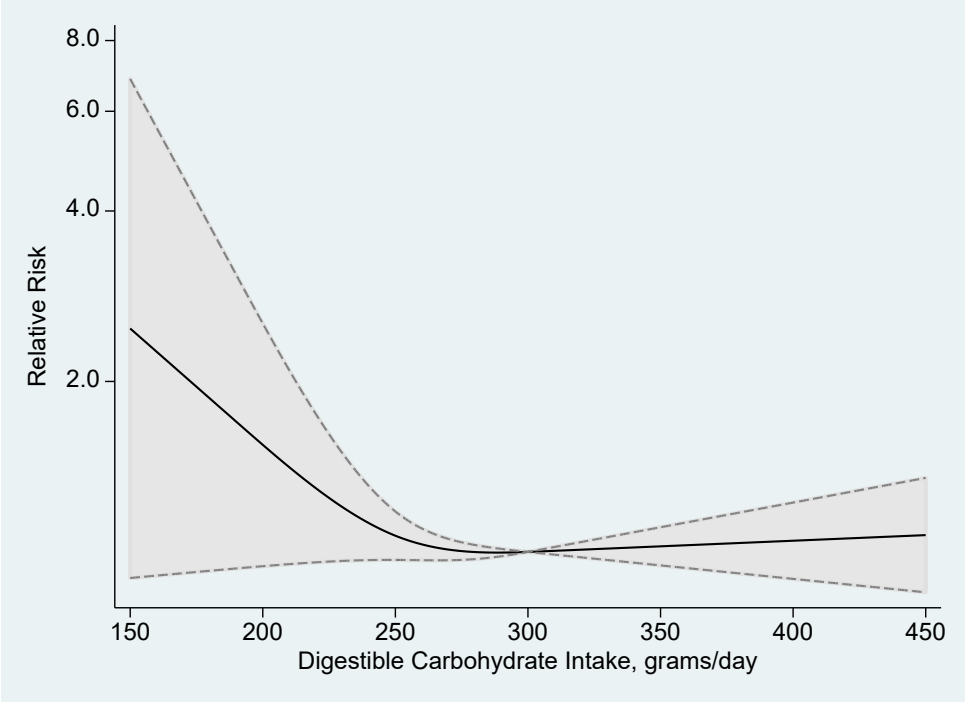
The Australian Longitudinal Study on Women's Health (ALSWH)[80] evaluated 9,899 Australian women aged between 50–55 years at baseline. After a 15-year followup, total digestible carbohydrate intake was found to be associated with a reduced risk of T2D. Compared with low carbohydrate intake (Quintile 1: <37.1% total energy intake), higher carbohydrate intake was associated with a significantly reduced risk of T2D (Quintile 2: 37.1% to 41% total energy intake, RR=0.50 95% CI: 0.28 to 0.89; Quintile 3: 41% to 44.3% total energy intake, RR=0.43, 95% CI: 0.22 to 0.83; Quintile 4: 44.3% to 48.1% total energy intake, RR=0.24; 95% CI: 0.11 to 0.55; Quintile 5: >48.1% total energy intake, RR=0.21; 95% CI: 0.07 to 0.57).

3.2.2.2.1. Dose-Response Meta-Analysis

The linear dose-response meta-analyses analyses showed no significant associations between digestible carbohydrate intake and incident T2D (per 10-gram per day increase: RR=0.96; 95% CI: 0.90 to 1.03; per 10% increase of total energy intake: RR=0.93; 95% CI: 0.78 to 1.11). The nonlinear dose-response analyses reflected a U-shaped association (Figure 9, $P_{nonlinearity}$=0.07; and Figure 10, $P_{nonlinearity}$=0.40). Analyzing carbohydrate intake as a percentage of total energy intake showed a gradual reduction in the risk of incident T2D up to 45% total energy intake. The risk then plateaued between 45% and 55% total energy intake before rising with higher carbohydrate intake levels. Similarly, analyzing carbohydrate intake in grams per day revealed a gradually reduced risk up to 270 grams per day, following by a plateau between 270 to 350 grams per day and increased risk after 350 grams per day (Appendix Table I.2.1and I.2.2).

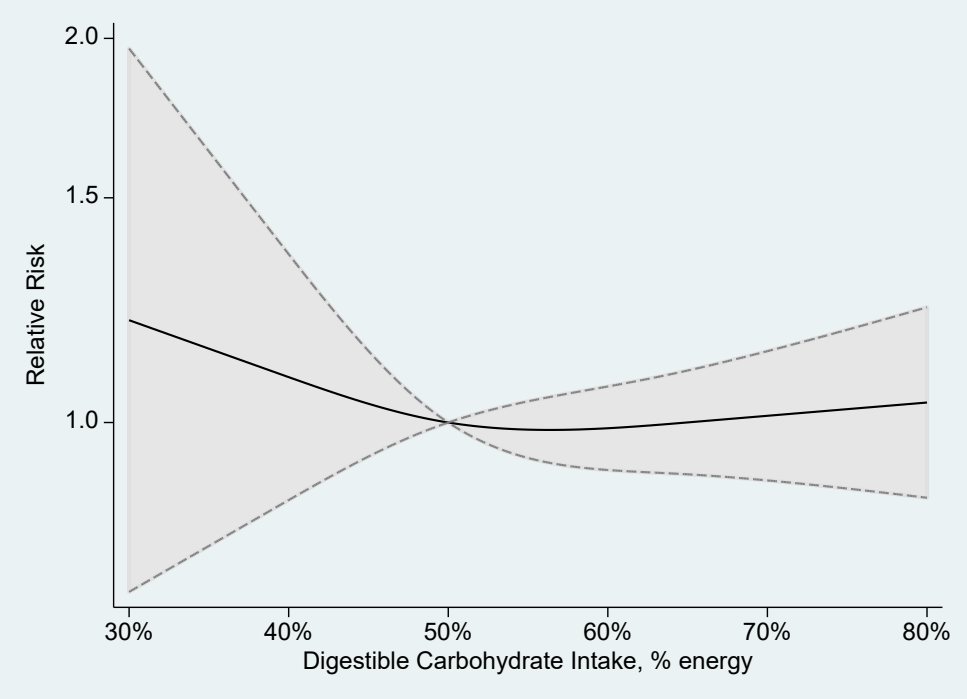
3. Results

Figure 9. Nonlinear dose-response relationship between the incidence of type 2 diabetes and digestible carbohydrate intake (grams per day)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

Figure 10. Nonlinear dose-response relationship between the incidence of type 2 diabetes and digestible carbohydrate intake (% total energy intake)



The solid line represents the nonlinear dose response, and the dotted lines represent the 95% confidence interval.

3.2.2.3. Key Question Results: Growth, Size, and Body Composition

Seven studies[42, 80, 83, 84] with 20,216 participants reported the association between digestible carbohydrate intake and changes in weight, and body composition. The median age of the participants was 51.2 years (range: 36.4–61.0 years). Digestible carbohydrate intake ranged from 35.2% to 63.2% for studies reporting percentage of total energy intake and 156 to 393 grams per day of carbohydrates for studies reporting grams per day.

The Australian Longitudinal Study on Women's Health (ALSWH)[80] evaluated 9,899 Australian women aged between 50–55 years. After a 15-year followup, the total digestible carbohydrate intake was associated with reduced risk of incident obesity, defined as BMI ≥ 30 kg/m^2. Compared with the lowest carbohydrate intake (Quintile 1: <37.1% total energy intake), higher digestible carbohydrate intake was associated with significantly reduced risk of obesity (Quintile 2: 37.1% to 41% total energy intake, RR=0.53 95% CI: 0.35 to 0.77; Quintile 3: 41% to 44.3% total energy intake, RR=0.14, 95% CI: 0.09 to 0.23; Quintile 4: 44.3% to 48.1% total energy intake, RR=0.07; 95% CI: 0.04 to 0.11; Quintile 5: >48.1% total energy intake, RR=0.01; 95% CI: 0.01 to 0.03).

The Tehran Lipid and Glucose Study (TLGS)[83] followed 1,915 healthy Iranian participants for a median of 8.91 years (interquartile range [IQR]: 7.98-9.69 years). The highest digestible carbohydrate intake (Tertile 3: median=63.2% total energy intake) was associated with significantly increased risk of weight gain, defined as ≥3% weight increase from baseline to the end of followup (HR=1.24, 95% CI: 1.02 to 1.51), compared with the lowest carbohydrate intake (Tertile 1: median=44.4% total energy intake).

In a 16-week randomized controlled trial, Kahleova et al.[42] evaluated 75 healthy participants with BMIs between 28 kg/m^2 and 40 kg/m^2. The percent energy from carbohydrate intake was significantly associated with reduced BMI ($p<0.001$), fat mass ($p<0.001$), and volume of visceral fat ($p=0.006$), as measured by Dual Energy X-ray Absorptiometry (DEXA).

Tammi et al.[84] conducted a pool analysis of three population-based prospective cohort studies: the Health 2000 and 2011 Health Examination Surveys (Health 2000), the Helsinki Birth Cohort Study (HBCS), and the Dietary, Lifestyle, and Genetic Determinants of Obesity and the Metabolic Syndrome (DILGOM) Study. A total of 8,327 Finnish adults aged between 25–70 years were followed for 7 years. The mean percent energy from carbohydrate intake from the three cohort studies ranged from 44% to 49%. There was no significant association between carbohydrate intake and the risk of weight gain of at least 5% from baseline.

3.2.2.4. Key Question Results: Strength of Evidence for Incident T2D and Body Weight

Table 6 summarizes strength of evidence evaluation for incident T2D and body weight.

Table 6. Strength of evidence of type 2 diabetes and body weight

Outcome	Effect	SOE	Rationale
Incident type 2 diabetes	11 studies[43, 80, 82, 85-87, 89-100] with 452,586 participants (median age of 52.5 years). • Nonsignificant associations with carbohydrate intake (per 10-gram per day increase: RR=0.96; 95% CI: 0.90 to 1.04; per 10% E: RR=0.93; 95% CI: 0.78 to 1.11). • Nonlinear association. • When carbohydrate intake was analyzed as the percentage of total energy intake, the risk reduced from low level of carbohydrate intake till until 45%E, remained relatively flat between 45%E and 55%E, and increased gradually from 55%E. • When carbohydrate intake was analyzed as grams per day, the risk reduced from low level of carbohydrate intake till until 270 grams per day, remained relatively flat between 270–350 grams per day, and increased gradually from 350 grams per day.	Low SOE	• Multiple large observational studies providing adjusted estimates. • No clear or consistent dose-response gradient or large effect. • Some inconsistency between primary studies due to variation in exposure levels and populations that can be partially explained in dose-response meta-analysis and subgroup analyses. • Wide confidence intervals or risk estimates across most of the intake range. • Serious risk of bias
Body weight	7 studies[42, 80, 83, 84] with 20,216 participants (median age of 51.2 years). • Inconsistent findings (in 2 risk of weight gain was reduced, in 1 risk of weight gain was increased, and in 4 there was nonsignificant change).	Insufficient SOE	• Very serious concern about inconsistency. • Serious risk of bias

Abbreviations: %E=percentage of total energy intake; CI = confidence interval; RR = relative risk; SOE = strength of evidence

3.2.2.5. Key Question Results: Surrogate Markers Suggesting Prediabetes or Abnormal Glycemia

Two studies[42, 88] reported surrogate markers associated with total digestible carbohydrate intake.

In a 16-week randomized controlled trial, Kahleova et al[42] evaluated 75 healthy participants with BMIs between 28 kg/m^2 and 40 kg/m^2. The percent carbohydrate intake from total energy was significantly associated with reduced Homeostasis Model Assessment (HOMA) index (p=0.04).

A prospective cohort study[88] recruited 325 pregnant Japanese women during weeks 8–15 of pregnancy. At weeks 24–28 of pregnancy, the highest digestible carbohydrate intake (Tertile 3: median=60.6% total energy intake) was found to be associated with a reduced risk of positive glucose challenge test, defined as a 1-hour plasma concentration ≥7.8 mmol/L after ingestion of 50 g glucose, compared with the lowest digestible carbohydrate intake (Tertile 1: median=49.5% total energy intake) (OR=0.46, 95% CI: 0.23 to 0.93).

3.2.3. Subgroup Analyses: Type 2 Diabetes

3.2.3.1. Sex

3.2.3.1.1. Women

Seven studies[86, 87, 89, 94, 96, 97, 99] reported the association between digestible carbohydrate intake and incident T2D exclusively among women. When high digestible carbohydrate intake was compared with low intake, the Shanghai Women's Health Study[96] reported significantly increased risk of T2D while the Australian Longitudinal Study[80] on Women's Health reported significantly reduced risk of incident T2D and incident obesity among women. Tajima et al. found that, among pregnant Japanese women, higher digestible carbohydrate intake was associated with reduced risk of positive glucose challenge test.[88]

3.2.3.1.2. Men

Seven studies[43, 86, 87, 89, 99, 100] reported the association exclusively among men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)[43] reported, among male smokers, higher carbohydrate intake was associated with significantly reduced risk of T2D. No other studies reported significant associations.

3.2.3.1.3. Dose-Response Meta-analyses

We found no significant linear dose-response relationship between carbohydrate intake and incident T2D in either men or women (Appendix Table J.3 an J.4). Appendix Figures K.4.1. and K.4.2. showed similar U-shaped nonlinear dose-response relationships in men and women, with the lowest risk at 48% total energy intake. However, we found significant nonlinear dose-response association ($P_{nonlinearity}$=0.01) only in men. The risk of incident T2D reduced until 0.45% total energy intake from digestible carbohydrate intake then then gradually increased with higher carbohydrate intake.

3.2.3.2. Geographic Locations

3.2.3.2.1. East Asia

Four studies[82, 86, 87, 100] conducted in East Asia reported the association between carbohydrate intake and incident T2D. Digestible carbohydrate intake ranged from 40.2% to 80.1% of total energy intake. One study, the Shanghai Women's Health Study[96] reported a significantly increased risk of T2D among 74,942 Chinese adult women. No other studies reported a significant association.

3.2.3.2.2. Western Countries

Seven studies[43, 80, 85, 90-95, 97, 98] conducted in western countries (i.e., Australia, the United States, and countries in Europe) reported the association between carbohydrate intake and incident T2D. Digestible carbohydrate intake ranged from 28.3% to 65.0% of total energy intake. Compared with low carbohydrate intake, high carbohydrate intake was associated with a reduced risk of T2D in men[43] and in women. [80]

3.2.3.2.3. Dose-Response Meta-Analysis

We found no significant linear dose-response association between carbohydrate intake and incident T2D in studies conducted in either East Asia or Western Countries (Appendix Table J.2). However, nonlinear dose-response relationships showed different patterns: in studies conducted in Western Countries, a U-shaped relationship was observed with initial reduction and then increased risk with increased intake , while in East Asian studies, there was initially increased risk, and then stable risk (Appendix Figure K.2.1and K.2.2).

4. Discussion

4.1 Key Findings and Strength of Evidence

4.1.1 Risk of Cardiovascular Disease

Cardiovascular disease (CVD) is the main cause of death in the United States. CVD risk factors are numerous and can be attributed to intrinsic factors like genetics as well as extrinsic factors like diet. Carbohydrates are an essential macronutrient that may affect CVD risk. We aimed to evaluate the isolated effect of digestible carbohydrates on the risk of cardiovascular diseases. We analyzed 21 prospective cohort studies that were conducted in Europe, East Asia, Australia, and United States. We found no eligible studies evaluated children (aged<18 years).

The analysis revealed a U-shaped nonlinear relationship between the intake of digestible carbohydrates and incident CVD risk. When carbohydrate intake was analyzed as percentage of total energy intake, the highest association was observed when daily carbohydrate intake exceeded 65% total energy intake, compared with the carbohydrate intake reference level of 50%. The carbohydrate intake associated with the lowest risk of CVD was 50% total energy intake. When carbohydrate intake was analyzed as grams per day, the highest association was observed when carbohydrate intake exceeded 300 grams per day, compared with the carbohydrate intake reference level of 300 grams per day. The amount of carbohydrates consumed that was associated with the lowest risk of CVD was 250 grams per day. When it comes to the risk of coronary heart disease (CHD), our study showed significant linear and nonlinear associations between carbohydrate intake and incident CHD. These associations become statistically significant when energy from carbohydrate consumption exceeds 50% of total energy intake.

The results also suggested a significant nonlinear association between carbohydrate intake and CVD-related mortality. The risk gradually decreased with higher carbohydrate intake until a consumption between 250 and 300 g of carbohydrate, after which the risk increased again. A similar trend was also observed when the risk was analyzed based on the percent energy intake, with the lowest risk associated with 55% total energy intake from carbohydrate intake.

Risk of stroke gradually increases when energy intake from carbohydrates exceeds 50% of total energy consumption. However, no significant association was found regardless of carbohydrate intake levels.

We found only a limited number of studies that met our inclusion criteria for surrogate markers for cardiovascular disease. The two studies that evaluated the effect of digestible carbohydrate intake on hypertension appeared to have conflicting results.[59, 80] However, this is likely due to the significant variation in the definition of "high carbohydrate intake" between the two studies. Although we were unable to conduct a meta-analysis, both studies indicate that a carbohydrate intake of between 48% and 55% was associated with a low risk of hypertension.

Two studies[56, 61, 71, 74] investigated the impact of carbohydrate intake on HDL cholesterol (HDL-C) and triglyceride levels. Both studies found that carbohydrate intake was negatively correlated with HDL-C levels and positively associated with higher levels of triglycerides. While, for low-density lipoprotein cholesterol (LDL-C), two studies with short followup found a tendency of lower LDL-C levels with higher carbohydrate intake.[56, 61, 71, 74] This effect was not apparent in a long-term U.S. study, the Coronary Artery Risk Development in Young Adults

study (CARDIA),[58] which found no significant association between the amount of digestible carbohydrates consumed and LDL-C level.

4.1.2 Risk of Type 2 Diabetes, Growth, Size, and Body Composition

This systematic review evaluated the association between dietary digestible carbohydrate intake and the incidence of type 2 diabetes (T2D), growth, size, and body composition. The spectrum of dysglycemia, such as impaired glucose tolerance, insulin resistance, and gestational diabetes were additional outcomes of interest. Seventeen studies[42, 43, 80, 82-100] with a total of 452,586 participants were included. Study participants were from Europe, East Asia, Australia, Middle East, and the United States.

Most studies showed no significant association between digestible carbohydrate intake and incident risk of T2D. However, the nonlinear dose-response meta-analyses showed a U-shaped association: the risk of T2D fell as carbohydrate intake increased, largely stabilized when carbohydrate intake was between 45%-55% of total energy intake and rose again beyond that amount. Similar findings were observed when analyzing carbohydrate intake in grams per day. The overall strength of evidence was low.

Only two studies met the criteria for the outcomes of prediabetes or surrogate markers suggesting dysglycemia.[42, 88] In one, carbohydrate intake was inversely associated with indices of insulin resistance. [41] In the other, the highest tertile of carbohydrate intake in pregnant women was associated with lower odds of a positive glucose challenge test.[88]

Subgroup analyses on sex (women vs. men) showed a similar nonlinear relationship between carbohydrate intake and incident T2D. There were clear regional differences in total carbohydrate consumption, reflecting traditional dietary patterns of that population. In East Asian countries, carbohydrate consumption ranged from 40–80% of total energy intake, while in Western countries, carbohydrates ranged from 30–70% of total energy intake. Low carbohydrate/ ketogenic style diets were excluded from this meta-analysis per the exclusion/inclusion criteria described above.

Four studies[42, 80, 83, 84] evaluated the association between digestible carbohydrate intake and changes in weight and other markers of body composition. With the small number of studies and conflicting findings, we were unable to draw clear conclusions.

4.2 Findings in Relation to What is Already Known

4.2.1 Risk of Cardiovascular Disease

While a recent systematic review[17] showed an increased risk of CVD (total cardiovascular events) when carbohydrate intake exceeded 60% of total energy intake, another review[18] suggested a minor but linear association between carbohydrate consumption and increased risk for CVD (RR of 1.1 with 95% CI of 1.03-1.17). In our meta-analysis that only included studies that explicitly reported digestible carbohydrate intake separate from fibers and other macronutrients, we found an absence of a linear association between carbohydrate consumption and the risk of CVD and demonstrated a nonlinear relationship that is likely U-shaped, with the lowest risk at or around 250 grams per day or 50% total energy intake from carbohydrates. In terms of CHD, systematic reviews by Qin et al.[18] and Mohammadifard et al.[20] did not suggest a significant association with dietary carbohydrates. Regarding the risk of stroke, a meta-analysis

conducted in 2015[101] pooled data from seven prospective cohort studies and demonstrated no association with high carbohydrate intake.

Our results regarding the association of carbohydrate intake with lower HDL-C and higher triglycerides are consistent with results of cross-sectional studies, which did not meet the inclusion criteria for the current systematic review.[24, 25, 102, 103] Some of these studies[24, 102, 103] suggested a decrease in LDL-C and total cholesterol (TC) levels associated with high carbohydrate diet, but with an increase in the TC to HDL-C ratio.[103] A recent systematic review[104] showed that a low-carbohydrate diet was associated with increased low-density LDL-c levels. However, this increase was not evident when the data from studies that were 6 months or longer followup were pooled.

4.2.2 Risk of Type 2 Diabetes, Growth, Size, and Body Composition

It is important to recognize that the key question, as posed, deliberately excluded all fiber-containing carbohydrate content from analysis. As such, only the contribution of digestible carbohydrates was analyzed. The evidence base of nutrition studies on carbohydrates is vast and heterogeneous, which makes comparisons between our results and previously published data more challenging. Acknowledging the limitations and low strength of evidence, our findings are congruent with current evidence that has not shown a significant association between digestible carbohydrates and the risk of T2D. Conversely, higher intake of fiber and minimizing intake of refined carbohydrates has been shown to decrease the risk of T2D and improve insulin sensitivity indices.[31, 105]

Baseline carbohydrate consumption is different in various parts of the world. The PURE study,[64] which assessed the association between carbohydrate and fat intake with CVD in 18 countries, showed that the percentage of consumed calories from carbohydrates ranges on average from 52% in Europe and North America to 65%–67% in China and South Asia. Our results showed a nonlinear relationship between carbohydrate consumption and the incidence of T2D, although the findings did not reach statistical significance. Interestingly, the phenomenon of the highest carbohydrate consumption being associated with increased risk of T2D, and moderate carbohydrate consumption being associated with lowest diabetes risk has been previously reported by the China Health and Nutrition Study in parts of the world with high baseline carbohydrate consumption, although that study was ineligible for this systematic review.[106] Our findings about weight changes and body composition were in general similar to a previously published meta-analysis,[107] which found no significant association between carbohydrate intake and obesity. However, most of the recent literature focuses on evaluating the quality of carbohydrates and the glycemic index, with much less literature addressing the intake of digestible carbohydrates.

4.3 Applicability

It is worth noting that the included studies in this systematic review are from different geographic locations and include cohorts with a wide range of eating habits and consumption of macronutrients. For example, in the Australian Longitudinal Study on Women's Health (ALSWH),[80] Quintile 1 of carbohydrate intake consisted of <37.1% of the energy intake from carbohydrates, and Quintile 5 had a carbohydrate intake of >48.1% of the energy intake from carbohydrates. Whereas the median carbohydrate intake in Quintile 1 for the Singapore Multi-Ethnic Cohort study (MEC)[57] was 46.6% of total energy, and Quintile 4 was >58.4% of total energy. We conducted dose-response meta-analysis to pool a wide range of carbohydrate intake

levels across eligible studies and avoided pairwise comparisons between higher quintiles and lower quintiles of carbohydrate intake. We also conducted subgroup analyses based on geographic locations. Furthermore, the included studies had a wide range of participants with varying ages, which made it challenging to synthesize evidence for specific age groups within the adult population. However, this variability in age makes the findings more relevant to a broader population.

The median followup period in the included studies was 10.7 years (range: 1 year–32 years). The long followup duration enabled us to better evaluate CVDs and T2D associated with digestible carbohydrate intake.

Although the evidence is growing in the adult population, there is still limited data in children on the direct effect of digestible carbohydrates on health outcomes. In our systematic review, we did not identify any eligible study that evaluated the impact of digestible carbohydrates in children and adolescents. This is, however, understandable, given the very low prevalence of outcomes of interest (e.g., CVD and stroke in the pediatric population). In a prospective cohort study,[108] Suissa et al. evaluated the effect of glycemic index and glycemic load on cardiovascular risk factors in children. The study found that glycemic index did not predict cardiometabolic risk factors, but the glycemic load did predict BMI, percent body fat, triglycerides, and HDL-C after 2 years, but not LDL-C, systolic blood pressure, or diastolic blood pressure.

Dietary strategies are the cornerstone of prevention and treatment of T2D. To date, the evidence has not supported using one macronutrient combination over another but instead emphasizes the importance of overall nutrient quality and calorie restriction where applicable. Our findings of there being no association between digestible carbohydrate intake and the risk of T2D lends continued support to this practice. As discussed, de-emphasizing the contribution of digestible carbohydrates may in fact allow for the focus to be on nutrients with proven benefit such as fiber-containing foods. Our study was not designed to answer questions regarding very low carbohydrate or ketogenic style diets, which warrant separate investigation.

It is important to emphasize that CVD and T2D intertwine clinically in many situations. For instance, the increased risk of cardiovascular mortality may, at least partially, be affected by unreported or under-reported increased incidence of T2D in the studied cohort.

4.4 Implications for Clinical and Policy Decisions

The results of these two systematic reviews will support the development of future guidance on a dietary reference intake (DRI) for carbohydrates. From a clinical standpoint, it is important to recognize that the quality of carbohydrate consumed (measured by glycemic index, glycemic load, dietary carbohydrate index, carbohydrate-fiber ratio, etc.) may play a major role in altering the risks associated with carbohydrate intake.[109, 110] For example, while some systematic reviews failed to establish an association between total carbohydrate consumption and coronary heart disease, some experts argue carbohydrate quality, not quantity, is what alters the risk of coronary heart disease.[111] Therefore, aside from the amount of digestible carbohydrates, clinicians should counsel patients about avoiding highly processed and refined foods and choosing better sources of carbohydrates such as fruits, vegetables, and whole grains.

4.5 Limitations and Suggestions for Future Research

The included studies adopted a wide range of dietary assessment methods, most commonly using food frequency questionnaires (FFQs). The validity of these instruments across the various

geographic locations of the included studies is unclear. The studies also used various recall periods, including longer than 3 months, which increases the risk of measurement bias. The included studies measured dietary intake once at baseline and then only at a few subsequent occasions, which was challenging. Ideally, longitudinal studies with multiple and frequent assessments are needed.

A major challenge in nutrition research is how to account for other nutrients that are co-existent in food. The whole food matrix, with its associated micronutrients and phytochemicals, is what is consumed and not individual macronutrients, and therefore drawing firm conclusions about any macronutrient can be difficult. In this systematic review, we extracted and synthesized results from the most adjusted model of individual studies, with the intention to control macronutrients to the fullest. However, most of the included studies only partially performed these adjustments. We were also unable to discern differences in carbohydrate quality, for example between simple carbohydrates (e.g., fructose from sugar-sweetened beverages) and more complex carbohydrates (e.g., starches from corn and potatoes) . This limitation is in part because of the varied methods for reporting dietary intake. Additionally, there is still no accepted consensus on how to define carbohydrate quality, although several proposals have been put forward. Variations in food consumption patterns and cooking approaches across the various locations of the available studies limits generalizability of results to other locations.

Length of study followup was also variable, ranging from 16 weeks to 32 years. Studies with short followup did not account for the variable rates of disease progression and may have underestimated the influence of digestible carbohydrate consumption in the long term. A rigorous long-term prospective study in a controlled feeding environment would answer these questions reliably, but due to practically, it is unlikely to be feasible. As intake over a lifespan may influence the development of these chronic diseases, studies following individuals throughout their lifespans would be ideal. However, a more feasible approach may be followup for at least 5-10 years. Such studies should also monitor weight stability and weight changes in addition to other lifestyle factors.

As studies that can obtain the outcome of interest are challenging given the long-term nature required, shorter term studies looking at surrogate markers will continue to be more feasible. However, very few studies reported intermediate outcomes or surrogate outcomes (e.g., LDL-C, HDL-C, glucose tolerance), partially due to lack of eligible clinical trials. Lastly, it is important to acknowledge the limitations of study-level meta-regression and dose-response meta-analysis, such as ecological bias, and particularly with a small sample size, the potential for large relative estimates that may not be biologically plausible.

Many questions remain regarding the impact of digestible carbohydrate intake on body composition. Future research is needed to separately evaluate the effect of starches, sugars, and fibers, as well as the level of processing comparing refined and unrefined carbohydrates, on weight and body composition. One question that frequently arises in clinical practice is the utility and role of low carbohydrate diets. Given the proportional change in other nutrient intake and inability to isolate digestible carbohydrates from other macronutrients, these studies were ineligible from this review. As interest in lower carbohydrate diets continues, consideration will need to be given on how to best assess the long-term safety and efficacy of these dietary patterns.

4.6 Conclusions

Dose-response meta-analyses suggest nonlinear relationship between the intake of digestible carbohydrates and CVD and incident T2D. These associations appear to be U-shaped. Evaluation

of the shapes of these associations demonstrates a certain range of carbohydrate intake that was associated with the lowest risk. These ranges can aid in developing future DRIs for carbohydrates, which can have important consequences on incidence and morbidity of chronic conditions and public health. The available literature suffers from serious limitations due to inadequate adjustment of confounding and inability to clearly isolate the effect of macronutrients from each other. The current results are subject to ecological bias because they are derived from aggregate data.

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Abbreviations and Acronyms

%E	Percentage of total energy intake
ALSWH	Australian Longitudinal Study on Women's Health
ARHQ	Agency for Healthcare Research and Quality
ATBC	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BMI	Body Mass Index
CARDIA	The Coronary Artery Risk Development in Young Adults
CHD	Coronary Heart Disease
CI	Confidence Interval
CVD	Cardiovascular Disease
CS-RFNCD	The Cohort Study on Risk Factors of Non-Communicable Diseases
DILGOM	The Dietary, Lifestyle, and Genetic Determinants of Obesity and the Metabolic Syndrome
DRI	Dietary Reference Intake
EPC	Evidence-based Practice Center
EPIC	The European Prospective Investigation into Cancer and Nutrition
FDA	Food and Drug Administration
FFQ	Food Frequency Questionnaires
GI	Gastrointestinal
HbA1C	Hemoglobin A1C
HBCS	The Helsinki Birth Cohort Study
HDL-C	High-Density Lipoprotein Cholesterol
Health 2000	The Health 2000 and 2011 Health Examination Surveys
HR	Hazard Ratio
HUSK	The Hordaland Health Study
J-MICC	The Japan Multi-Institutional Collaborative Cohort
KARE	The Korean Association Resource
KQ	Key Questions
LDL-C	Low-Density Lipoprotein Cholesterol
MHRA	Medicines and Healthcare Products Regulatory Agency
MEC	Multi-Ethnic Cohort study
NAFLD	Nonalcoholic Fatty Liver Disease
NIPPON DATA	The National Integrated Project for Prospective Observation of Non-communicable Communicable Disease and its Trends in the Aged
NLP	Natural Language Processing
OR	Odds Ratio
PICOTS Design	Population, Intervention, Comparator, Outcome, Timing, Setting/Study

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized Controlled Trials
RDA	Recommended Dietary Allowance
ROBINS-I	Risk Of Bias In Non-Randomized Studies - of Intervention
RR	Relative Risk
SD	Standard Deviation
SEADS	Supplemental Evidence and Data for Systematic Reviews
SEASONS	The Seasonal Variation in Blood Cholesterol Levels Study
SOE	Strength of Evidence
T2D	Type 2 Diabetes
TC	Total Cholesterol
TEP	Technical Expert Panel
TOO	Task Order Officer
U.K.	United Kingdom
U.S.	United States
WHO	World Health Organization