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Impact of individual and environmental factors on dietary or lifestyle interventions to prevent type 2 diabetes development: a systematic review

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Abstract

Background The variability in the effectiveness of type 2 diabetes (T2D) preventive interventions highlights the potential to identify the factors that determine treatment responses and those that would benefit the most from a given intervention. We conducted a systematic review to synthesize the evidence to support whether sociodemographic, clinical, behavioral, and molecular factors modify the efficacy of dietary or lifestyle interventions to prevent T2D.

Methods We searched MEDLINE, Embase, and Cochrane databases for studies reporting on the effect of a lifestyle, dietary pattern, or dietary supplement interventions on the incidence of T2D and reporting the results stratified by any effect modifier. We extracted relevant statistical findings and qualitatively synthesized the evidence for each modifier based on the direction of findings reported in available studies. We used the Diabetes Canada Clinical Practice Scale to assess the certainty of the evidence for a given effect modifier.

Results The 81 publications that met our criteria for inclusion are from 33 unique trials. The evidence is low to very low to attribute variability in intervention effectiveness to individual characteristics such as age, sex, BMI, race/ethnicity, socioeconomic status, baseline behavioral factors, or genetic predisposition.

Conclusions We report evidence, albeit low certainty, that those with poorer health status, particularly those with prediabetes at baseline, tend to benefit more from T2D prevention strategies compared to healthier counterparts. Our synthesis highlights the need for purposefully designed clinical trials to inform whether individual factors influence the success of T2D prevention strategies.

Plain language summary

Clinical trials to prevent development of type 2 diabetes (T2D) that test dietary and lifestyle interventions have resulted in different results for different study participants. We hypothesized that the differing responses could be because of different personal, social and inherited factors. We searched different databases containing details of published research studies investigating this to look at the effect of these factors on prevention of the development of T2D. We found a small amount of evidence suggesting that those with poorer health, particularly those with a higher amount of sugar in their blood, tend to benefit more from T2D prevention strategies compared to healthier counterparts. Our results suggest that further clinical trials that are designed to examine the effect of personal and social factors on interventions for T2D prevention are needed to better determine the impact of these factors on the success of diet and lifestyle interventions for T2D.

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Diabetes affects over 530 million people worldwide[1]. Around 90% of all diabetes is estimated to be type 2 diabetes (T2D), a non-autoimmune condition with marked pathophysiological heterogeneity[2]. In many cases, diet and physical activity interventions targeted at bodyweight reduction or preventing weight gain have demonstrated to delay progression[3–6], yet T2D remains a major cause of morbidity and mortality globally[7]. Chronic inadequate control of hyperglycemia causes downstream microvascular and macrovascular complications that drive the costly and debilitating T2D public health burden[7]. Coupled with its increasing incidence, public health and clinical efforts need to optimize effective upstream strategies for T2D prevention.

Landmark randomized intervention trials have demonstrated the effectiveness of intensive lifestyle interventions and glucose-lowering drug therapies for delaying the onset of T2D in patients at high risk[3–6]. However, T2D incidence has only escalated in the decades since, despite the success of early clinical trials. Thus, implementation strategies for diabetes prevention in the real-world setting involving more practical ways of identifying high-risk individuals and precision prevention research may contribute to understanding this gap[8].

Precision prevention of T2D serves to minimize an individual's T2D risk factor profile and maximize the effectiveness of new or established strategies for disease prevention through targeting biological interactions and/or removing barriers to access and adherence to lifestyle modification[9]. For example, precision prevention approaches might use clinical (e.g., age, sex, body mass index [BMI]), social (e.g., education attainment, socioeconomic status), or molecular (e.g., genetic, 'omic' traits) characteristics to inform strategies likely to elicit the most effective or sustainable response for an individual, resulting in tailored prevention strategies[9–11].

The purpose of this systematic review is to critically appraise the accumulated experimental evidence underpinning the feasibility and effectiveness of the clinical translation of precision prevention of T2D. The scope of our investigation included studies reporting the effect modification of lifestyle and dietary interventions for T2D prevention by any of the following individual-level factors, including sociodemographics, clinical risk factors, behavior, or molecular traits. This work was undertaken as part of a series of systematic reviews conducted by the ADA/EASD Precision Medicine in Diabetes Initiative[12], an international collaboration of global leaders in precision diabetes medicine[13].

Through this systematic review, we found low certainty evidence that those with poorer health status, particularly those with prediabetes at baseline, tend to benefit more from T2D prevention strategies compared to healthier counterparts. Clinical trials specifically designed to inform whether individual factors influence the success of T2D prevention strategies are needed in the future.

Methods

The systematic review protocol was pre-registered on the International Prospective Register of Systematic Reviews (PROSPERO; CRD42021267686).

Data sources and search. Our search included MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases for studies reporting on the efficacy of lifestyle or behavioral interventions with T2D incidence, published from 1/1/2000 to 7/15/2021. Lifestyle interventions were defined as interventions ranging from interventions on single behavioral factors including diet, physical activity, smoking, and body weight loss, to multi-component modification programs focused on different behavioral components. An experienced librarian developed a search strategy (Supplementary Note 1), which included combinations of keywords related to lifestyle intervention for preventing T2D (diet, lifestyle, physical activity, body weight), study design, and health outcome, and was limited to the English language. We also scanned the references of included manuscripts and the reference list of systematic reviews published within the past 2 years to identify additional relevant studies.

Study selection. We included studies reporting the effect of a lifestyle, dietary pattern, or dietary supplement interventions vs. other active comparators or control on the incidence of T2D and reporting the results stratified by any eligible factor. Lifestyle interventions included either single-component (exercise, smoking, education through text messaging to the mobile phone, etc) or multi-component modification programs involving weight loss through diet or supplementation, physical activity, awareness education etc. Eligible stratification factors, or effect modifiers, included individual-level sociodemographic (i.e., race/ethnicity, socioeconomic status/education, location, age, sex), clinical factors (i.e., BMI, dysglycemia, presence of comorbidities), behavioral (i.e., baseline diet, physical activity) or molecular traits (i.e., genetics, metabolites). We did not review population-level exposures such as built environment, pollution, or climate. Off-label pharmaceutical interventions and bariatric surgery were beyond the scope of the review. We limited inclusion to studies in adults aged >18 years and enrolling at least 100. We included non-randomized and randomized clinical studies delivering an eligible intervention, comparing against another active intervention, usual care, placebo control, or non-control group. The majority of studies ($N = 76$ or 94%) included in this review are RCTs to examine the effect on the intervention on T2D incidence. However, as our focus is on the modification of the intervention effect by sociodemographic, clinical, behavioral and molecular factors, none of these trials can be considered randomized for the purpose of this review, as the randomization block is not conserved. Studies exclusively among individuals with a current or history of gestational diabetes were excluded because they overlapped in scope with another PMDI consortium review.

Screening, data extraction, and quality assessment. We used the Covidence online systematic review platform[14] for literature screening, data extraction, and consensus. Screening consisted of two stages: (1) title and abstract and (2) full text. At each screening stage, two independent reviewers determined the eligibility of the citation, and in the case of disagreement, a third reviewer resolved the discrepancy. Among the full papers accepted for inclusion in the review, two independent reviewers extracted detailed information on the study design, participant characteristics, interventions, comparators, effect modifiers, follow-up for T2D, and analytic approach. We extracted findings related to the effect modification of treatment vs. comparator on T2D risk, including strata-specific treatment groups' T2D cases and incidence rates, or strata-specific treatment-comparator incidence rate ratios, relative risks, risk differences, etc., including measures of variance. We also extracted data on different available measurements for the interaction of the effect modifier with the intervention effect on T2D, including interaction term estimates, interaction term p-value, stratified estimates, heterogeneity test and noted any text referring to tests performed with "data not shown". We developed and piloted the data extraction template (Supplementary Table 1), and discrepancies were ruled on by a third reviewer. The relevant statistical results extracted for each effect modifier has been provided as Supplementary Data 1.

We evaluated the studies' risk of bias using a modified JBI Critical Appraisal Checklist for randomized controlled trials[15], performed by two independent reviewers and disagreements resolved by a third reviewer. We modified the 13-item checklist to 9 questions tailored to evaluating the quality of the study design but with consideration for our primary interest in stratified results rather than the total intervention effect for T2D risk. These 9 questions were mainly based on randomization, interventions, treatment, and assessor blindness to outcome assessment. Our evaluation corresponded to color coding in a heat map organized by intervention type and effect modifier (Supplementary Fig. 1).

Synthesis of results. We collated the literature according to intervention type as lifestyle intervention programs (single or multi-component), dietary pattern interventions (involving modifications in diet only), or supplement intervention and effect modifier analyzed (e.g., sex, age strata) to synthesize results. We determined that a meta-analysis was not feasible among the studies included in our review due to paucity and marked differences in the nature of the study populations, interventions and comparators, study designs, and effect modifiers analyzed. We qualitatively evaluated the direction and magnitude of results and statistical tests among each prevention strategy for each effect modifier. We weighed these qualitative and quantitative results against their risk of bias. We qualitatively synthesized the evidence for each modifier based on the direction of findings reported in available studies. We used the Diabetes Canada Clinical Practice Scale to assess the certainty of the evidence for a given effect modifier[16]. A level of evidence was assigned following the approach and criteria described in Supplementary Table 2. For example, higher levels were assigned if the study was a systematic overview or meta-analysis of high-quality RCTs or an appropriately designed RCT with adequate power to answer the question posed by the investigators. Then, each recommendation was assigned a grade from A to D. Two reviewers independently assessed the certainty of the evidence and resolved disagreements through consensus discussion.

Reporting summary. Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

The results of our systematic literature search are presented in the Fig. 1 PRISMA flow diagram. Of the 10,880 citations identified through database searches and other sources, 1047 abstracts were retrieved for full-text review. From these, 81 publications met our inclusion criteria, and data were extracted.

Study characteristics. The 81 publications included in our review represented 33 unique intervention studies (Table 1 and Supplementary Table 3). Twenty-eight studies were randomized clinical trials (RCTs), three were nonrandomized parallel group trials, and two were single-arm clinical interventions. Fourteen intervention studies took place in Asia, 11 in Europe, seven in North America, and one was a multicenter study that took place in Asia and Europe. Intervention enrollment sample sizes ranged from 302 to 48,835 participants (Table 1). Twenty-two studies included individuals at high risk for T2D, two studies at increased cardiovascular risk, and other studies included the general population or other specific groups. The active intervention times ranged from one lifestyle counseling visit to active interventions lasting up to 10 years (Supplementary Fig. 2).

Twenty-four of the included studies assessed the effect of a multi-component lifestyle intervention program focused on changes in diet, physical activity, smoking, or body weight loss. Four studies implemented a dietary intervention, and five administered supplements. Across multi-component lifestyle intervention studies, the comparator consisted of a less intensive lifestyle program consisting of usual care or general lifestyle advice administered at baseline. Active comparator groups for

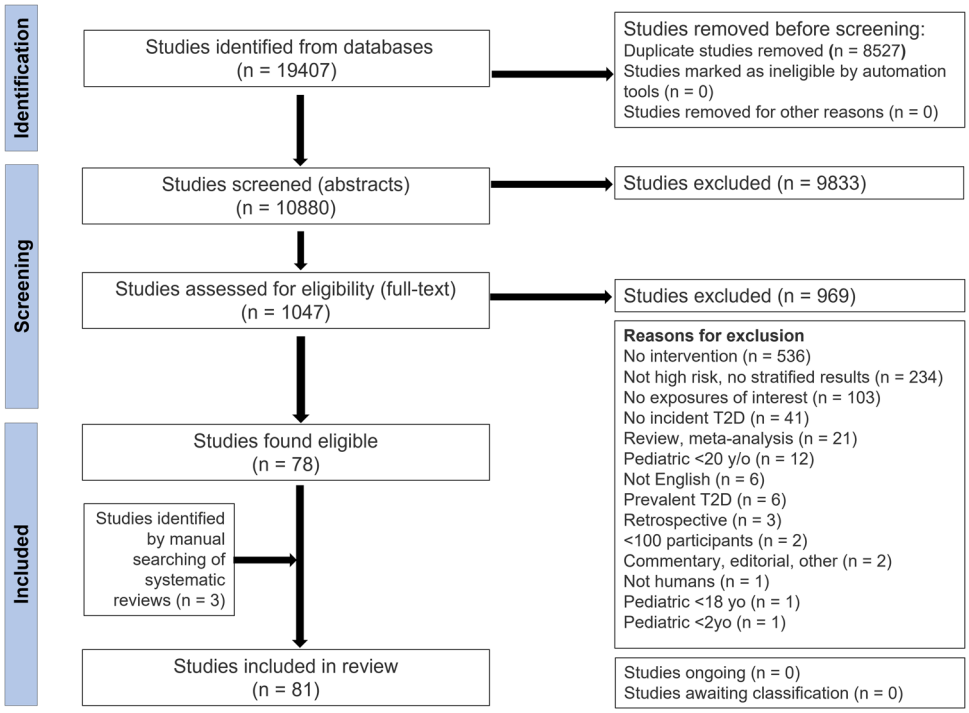


Fig. 1 PRISMA flow diagram. Stepwise screening stages adapted for selecting the studies of interest using Covidence software. Screening at all stages was done by two independent reviewers, and a third reviewer resolved conflicts.

Table 1 Description of study population and study design of the included trials grouped according to the type of intervention.

	Study population		Study design					Main trial info PMIDs	Included studies (PMDIs)
Trial/Study name	**Country**	**Total enrolled; inclusion criteria**	**Baseline enrollment years**	**Intervention design**	**Active intervention duration**	**Intervention(s)**	**Comparator/control intervention**		
Lifestyle interventions									
Chae et al.[27]	South Korea	*N* = 7233; General population	2007/11	Non-randomized, parallel arm	6 months	Physical activity program	Usual care	22688549[27]	22688549[27]
Da Qing IGT and Diabetes Study	China	*N* = 577; Prediabetes	1986	Cluster-randomized trial	6 years	(i) Diet: Low-calorie, low-fat (25–30% kcal) healthy pattern; (ii) Increase exercise; (iii) Diet + Exercise	Provided with diabetes education materials at baseline	9096977[5]	24731674[28], 34212465[17], 12413779[29]
Diabetes Community Lifestyle Improvement Program (D-CLIP)	India	*N* = 578; Prediabetes	2009/12	Randomized, parallel arm	3 years	Lifestyle diabetes prevention program + Metformin	Lifestyle diabetes prevention program at baseline	27504014[18]	27504014[18]
Diabetes in Europe—Prevention using Lifestyle, Physical Activity and Nutritional - Catalonia (DE-PLAN-CAT)[a]	Spain	*N* = 544; Prediabetes	2006	Non-randomized, parallel arm	4 years	Lifestyle weight loss and diabetes prevention program	Provided with diabetes education materials at baseline	22322921[30]	22322921[30]
Diabetes Prevention Program (DPP)[a]	US	*N* = 3234; Prediabetes	1996/99	Randomized, parallel arm	Mean 2.8 years	(i) Lifestyle weight loss and diabetes prevention program; (ii) Metformin	Usual care + placebo	11832527[3]	26024851[31]; 33444158[32]; 33317629[33]; 28453780[34]; 19640960[35]; 23860722[36]; 16855264[37]; 19017751[38]; 18060660[39]; 11832527[3]; 23512951[40]; 17077202[41]; 19878986[42]; 33394545[43]; 29021207[44]; 21378175[45]; 20682687[46]; 17363740[47]; 25697494[48]; 25277389[49]
EDIPS-Newcastle	UK	*N* = 102; Prediabetes		Randomized, parallel arm	5 years	Lifestyle diabetes prevention program	Usual care	19758428[50]	23451166[51]
Finnish Diabetes Prevention Study (DPS)[a]	Finland	*N* = 522; Prediabetes	1993/98	Randomized, parallel arm	Mean 3.2 years	Lifestyle and weight loss diabetes prevention program	Provided with diabetes education materials at baseline	11333990[4]	16759313[52]; 17277585[53]; 16873699[54]; 18249219[55]; 19651919[56]; 17636114[57]; 11333990[4]; 20980412[58]; 12145174[59]; 15127203[60]; 18252900[61]; 15616024[62]; 15309292[63]; 15983230[64]; 18091023[65]; 15126514[66]; 17437080[67]
Indian Diabetes Prevention Program 2013 (IDPP-2013)	India	*N* = 537; Men with prediabetes	2009	Randomized, parallel arm	24 months	SMS-delivered lifestyle diabetes prevention education	Provided with diabetes education materials at baseline	24622367[68]	26773871[69]; 16391903[6]

Table 1 (continued)

Trial/Study name	Study population		Study design					Main trial info PMIDs	Included studies (PMDIs)
	Country	Total enrolled; inclusion criteria	Baseline enrollment years	Intervention design	Active intervention duration	Intervention(s)	Comparator/control intervention		
Indian Diabetes Prevention Programme (IDPP-1)	India	$N = 531$; Prediabetes	2001/02	Randomized, parallel arm	3 years	(i) Lifestyle diabetes prevention program; (ii) Metformin; (iii) Lifestyle + Metformin	Usual care	16391903[6]	16391903[6], 20519663[70], 26773871[69]
Indian Diabetes Prevention Programme (IDPP-2)	India	$N = 407$; Prediabetes	2003/05	Randomized, parallel arm	3 years	Lifestyle diabetes prevention program + Pioglitazone	Lifestyle diabetes prevention program + Placebo	19277602[71]	20519663[70]
Japan Diabetes Prevention Program (Japan DPP)[a]	Japan	$N = 304$; Prediabetes	1999/02	Randomized, parallel arm	3 years	Lifestyle weight loss and diabetes prevention program	Provided with diabetes education materials at baseline	25452854[72]	25452854[72]; 21235825[20]
Kerala Diabetes Prevention Program (K-DPP)	India	$N = 1007$; Prediabetes, rural	2013	Cluster-randomized trial	12 months	Peer-led lifestyle diabetes prevention program	Provided with diabetes education materials at baseline	24180316[73]	29874236[74]
Kosaka et al.[a][75]	Japan	$N = 458$; Men with prediabetes	1990/92	Randomized, parallel arm	4 years	Lifestyle weight loss and diabetes prevention program	Lifestyle weight loss and diabetes prevention information only	15649575[75]	15649575[75]
Let's Prevent Diabetes	UK	$N = 880$; Prediabetes	2009/11	Cluster-randomized trial	36 months	Lifestyle diabetes prevention program	Provided with diabetes education materials at baseline	22607160[76]	26740346[77]
Multiple Risk Factor Intervention Trial (MRFIT)	US	$N = 12,866$; Men with high cardiovascular risk	1973/76	Randomized, parallel arm	6 years	Lifestyle modifications for heart disease prevention	Usual care	15738450[78]	15738450[78]
Nanditha et al. [79]	India, UK	$N = 2062$; Prediabetes	2012/17	Randomized, parallel arm	24 months	SMS-delivered lifestyle diabetes prevention education	Provided with diabetes education materials at baseline	31919539[79]	31919539[79]
National Program for the Prevention of Type 2 Diabetes (FIN-D2D)[a]	Finland	$N = 2798$; Prediabetes	2004/07	Population-wide intervention	Mean 14 months	Lifestyle weight loss and diabetes prevention program	-	20664020[80]	22983785[81]; 33771515[82]; 21781153[83]; 20664020[80]; 21622677[84]
Niyantrita Madhumeha Bharata Abhiyaan (NMB-Trial)	India	$N = 4450$; Prediabetes	2017	Cluster-randomized trial	3 months	Yoga-based lifestyle diabetes prevention program	Presentation on lifestyle for diabetes prevention at baseline	34177805[85]	34177805[85]
Norfolk Diabetes Prevention Study (NDPS)	UK	$N = 1028$; Prediabetes	2011/18	Randomized, parallel arm	12–46 months	(i) Lifestyle diabetes prevention program; (ii) Lifestyle diabetes prevention program with peer support	Provided with diabetes education materials at baseline	33136119[86]	33136119[86]
Prevention of Diabetes in Euskadi (PreDE)[a]	Spain	$N = 1088$; Prediabetes	2011/13	Cluster-randomized trial	24 months	Lifestyle weight loss and diabetes prevention program	Usual care	29476888[87]	29476888[87]
Tehran Lipid and Glucose Study (TLGS)	Iran	$N = 10,368$; General population	1999/01	Non-randomized, cluster	Mean 3.6 years	Lifestyle program for chronic disease prevention	Usual care	20494239[88]	25029368[89]; 20494239[88]
Thai Diabetes Prevention Program (Thai DPP)	Thailand	$N = 1903$; Prediabetes	2013	Cluster-randomized trial	24 months	Lifestyle diabetes prevention program	Provided with diabetes education materials at baseline	31079517[19]	31079517[19]
Västerbotten Intervention Programme (VIP)	Sweden	$N = 113, 203$; General population	1987-present	Population-wide intervention	Ongoing	Lifestyle CVD and diabetes prevention program	-	20339479[90]	25532678[91]
Zensharen Study for Prevention of Lifestyle Diseases[a]	Japan	$N = 641$; Prediabetes	2004/06	Randomized, parallel arm	36 months	Lifestyle weight loss program + Frequent engagement	Lifestyle weight loss program + Minimal engagement	21824948[92]	21824948[92]
Dietary pattern interventions									
CORonary Diet Intervention with Olive oil and cardiovascular PREVention study (CORDIOPREV)	Spain	$N = 1002$; Prevalent heart disease	2009/12	Randomized, parallel arm	Median 7 years	Mediterranean dietary pattern	AHA low-fat pattern (<30% kcal)	27297848[93]	32723508[94]

Table 1 (continued)

	Study population		Study design					Main trial info PMIDs	Included studies (PMDIs)
Trial/Study name	**Country**	**Total enrolled; inclusion criteria**	**Baseline enrollment years**	**Intervention design**	**Active intervention duration**	**Intervention(s)**	**Comparator/control intervention**		
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts (PREDIMED)	Spain	*N* = 7447; High cardiovascular risk	2003/09	Randomized, parallel arm	4.8 years	(i) Mediterranean pattern + extra-virgin olive oil; (ii) Mediterranean pattern + mixed nuts	Low-fat pattern	29897866[95]	29663011[96], 26739996[97]; 23034962[98]; 31377179[99]; 24573661[100]; 20929998[101]
Shahbazi et al. [102]	Iran	*N* = 336; Prediabetes	2012	Randomized, parallel arm	2 years	(i) High-fat diet from olive oil (45% kcal); (ii) Normal fat diet (30% kcal)	Standard low-fat diet (<30% kcal)	DOI 10.1007/s13410-017-0548-3	DOI 10.1007/s13410-017-0548-3[102]
Women's Health Initiative Dietary Modification Trial (WHI-DM)	US	*N* = 48,835; Healthy postmenopausal women	1993/98	Randomized, parallel arm	Mean 8.1 years	Low-fat (20% kcal) healthy pattern	Provided with healthy diet materials at baseline	18663162[103]	29282203[104]
Dietary supplement interventions									
Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study (ATBC)	Finland	*N* = 29,133; Men, smokers	1985/88	Randomized, parallel arm	Median 6.1 years	2 × 2 factorial: (i) alpha-tocopherol (50 mg/day), (ii) beta-carotene (20 mg/day)	Placebo	8205268[105]	17994292[106]
Vitamin D and Type 2 Diabetes Trial (D2d)	US	*N* = 2423; Prediabetes	2013/17	Randomized, parallel arm	Median 2.5 years	Vitamin D supplementation (4000 IU/day)	Placebo	31173679[107]	31173679[107]
Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS)	US	*N* = 5442; Women with cardiovascular disease	1998	Randomized, parallel arm	Median 7.3 years	Folic acid (2.5 mg/day), vitamin B6 (50 mg/day), and vitamin B12 (1 mg/day) combined supplementation	Placebo	19491213[108]	19491213[108]
Women's Antioxidant Cardiovascular Study (WACS)	US	*N* = 8171; Women with cardiovascular disease	1995/96	Randomized, parallel arm	Median 9.2 years	2 × 2 × 2 factorial: (i) vitamin C (500 mg/day), (ii) vitamin E (600 IU/day), (iii) beta-carotene (50 mg/eod) supplementation	Placebo	19491386[109]	19491386[109]
Women's Health Study (WHS)	US	*N* = 39,876; Healthy women	1992/95	Randomized, parallel arm	10.1 years	2 × 2 Factorial, every other day: Aspirin (100 mg); (ii) Vitamin E supplementation (600 IU)	Placebo	15998891[110]	17003353[111]

[a]Trials which aimed at weight loss and prevention of T2D.

Table 2 Efficacy of T2D preventive interventions according to sociodemographic effect modifiers.

Modifier	T2D preventive strategies								
	Lifestyle intervention			Dietary pattern intervention			Dietary supplements intervention		
	Number of studies	Effect modification[a]	Certainty of evidence[b]	Number of studies	Effect modification[a]	Certainty of evidence[b]	Number of studies	Effect modification[a]	Certainty of evidence[b]
Age	12	Yes: 7 studies No: 5 studies	Grade D	3	No: 3 studies	Grade D	4	Yes: 1 study No: 3 studies	Grade D
Sex	16	Yes: 1 study No: 15 studies	Grade D	2	No: 2 studies	Grade D	1	Yes: 1 study	Grade D
Race/ethnicity	3	No: 3 studies	Grade D	1	No: 1 study	Grade D	1	No: 1 study	Grade D
Socioeconomic status/ Education	4	Yes: 1 study No: 3 studies	Grade D	-	-	-	-	-	-
Location	2	No: 2 studies	Grade D	-	-	-	1	No: 1 study	-

Overview of the included studies investigating whether sociodemographic factors modify the response to T2D preventive intervention strategies.
[a]Yes/No corresponds to significant/nonsignificant effect modification, as reported in the study.
[b]Certainty of evidence denotes consistency, Grading based on Diabetes Canada scale A to D.

dietary intervention studies focused on high-fat diets consisted of a low-fat intervention. The active comparator for supplement studies consisted of a placebo intervention. T2D was diagnosed in person with an oral glucose tolerance test (OGTT) in 27 studies, whereas in 6 studies, T2D was ascertained via self-report or through linkage with a healthcare registry database. The primary endpoint was T2D incidence in 21 studies or a composite cardiovascular event in six studies (Table 1 and Supplementary Table 3).

All except seven studies of a multi-component lifestyle intervention program showed evidence that a lifestyle intervention reduces the risk of T2D, with estimated relative risk reduction ranging from 60 to 23% (Supplementary Table 3). Available evidence also suggests that a high-fat diet (Mediterranean pattern diet with extra-virgin olive oil/ mixed nuts or high-fat diet from olive oil), reduces the relative risk of T2D when compared to a diet with a lower amount of fat. Evidence from studies using supplements showed a null effect on T2D risk reduction.

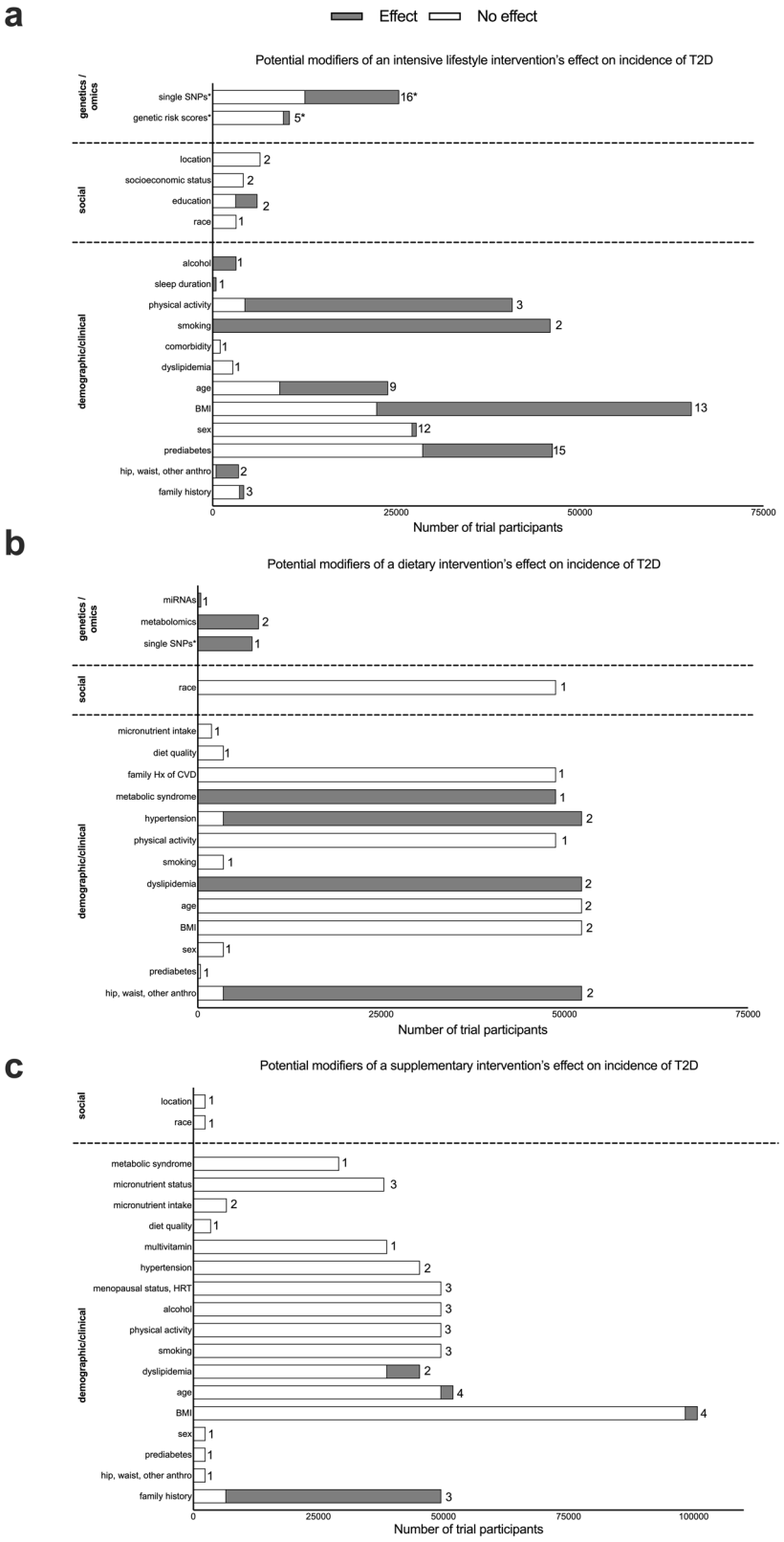
Our certainty of evidence assessment determined that the primary study design and approach was generally low, particularly for the RCTs, owing to randomization methods and uniform outcome assessment (Supplementary Fig. 1). However, common concerns for bias were due to non-blinding of participants, deliverers, and outcomes assessors to treatment assignment. Nonrandomized interventions and RCTs having additional concerns for study design did have ratings of high risk of bias.

Sociodemographic and clinical factors. Some clinical trials, such as the Diabetes Prevention Program (DPP), the Finnish Diabetes Prevention Study (DPS), or the PREDIMED study, were highly represented, with 20, 16, and 6 different publications from each study, respectively. Certainty of evidence to indicate different effects for sociodemographic and clinical characteristics such as age, sex, race/ethnicity, socioeconomic status or geographic location in response to lifestyle intervention was low. Study-specific numeric estimates for the effect modification are provided in the extended data file. Evidence from studies investigating sociodemographic interaction effects in dietary modification or supplementation trials showed no significant heterogeneity in response to intervention according to these characteristics (Table 2 and Fig. 2).

Fourteen studies investigated whether BMI modified the efficacy of multi-component lifestyle interventions. Nine of these studies showed that BMI is not associated with different responses to a lifestyle program, but five studies showed suggestive evidence that individuals with low BMI could benefit most from a lifestyle intervention. Four of these five studies presenting evidence of the differential effect of a lifestyle intervention according to BMI were conducted in Asia (Table 3). No appreciable evidence for interactions with BMI was observed in studies that implemented a dietary or supplement intervention (Table 3). Eighteen studies tested the efficacy of an intensive lifestyle intervention for preventing T2D stratified based on baseline glucose levels, impaired glucose tolerance, or prediabetes status. Evidence presented in eight of these studies indicated statistically different effects based on baseline dysglycemia, but other studies did not find evidence of effect modifications. Three studies investigated family history of T2D as a potential lifestyle intervention effect modifier, and only one provided suggestive evidence of heterogenous treatment responses. Studies stratified by baseline cardiometabolic risk factors reported that individuals with poorer health status, particularly those with dyslipidemia and metabolic syndrome, tend to benefit more from dietary or supplement interventions than healthier individuals (Table 3).

Behavioral factors. Several secondary studies have assessed whether baseline lifestyle factors (i.e., overall dietary quality, alcohol intake, physical activity, and/or smoking) influence the efficacy of T2D prevention interventions. Evidence presented in studies investigating the effect of a lifestyle intervention according to baseline smoking status and physical activity indicates statistically different effects, suggesting that smokers and those with lower physical activity levels benefited less from a lifestyle program (Table 4). Available studies reported no interactions of baseline smoking status and physical activity levels with dietary or supplement interventions on the risk of T2D. Among the four studies that focused on alcohol intake, only one found that the lifestyle intervention was more effective in individuals who drink alcohol frequently than in those who rarely drink. Six studies tested whether baseline diet modified the association between supplements and the risk of T2D and found no evidence of significant interactions (Table 4).

Molecular factors. The extent to which genetic predisposition modifies the efficacy of interventions to prevent T2D was reported in 22 publications. Most of them were based on data



from the DPP and the DPS. Genetic predisposition was defined based on single genetic variants in 17 studies or genetic risk scores in five. While many of the T2D-associated loci identified in the earlier GWAS studies have been examined for their potential roles as effect modifiers, some reported evidence that individuals with specific genotypes could benefit the most from a lifestyle intervention, but these studies rarely corrected for the number of performed tests. Of the five studies that reported on the role of polygenic scores for T2D, only one study showed that lifestyle intervention was more effective among individuals with a high genetic risk.

Besides genetics, other molecular markers such as plasma branched-chain amino acids and miRNAs have been studied. The evidence that these molecular features modify the efficacy of

Fig. 2 Potential effect modifiers of lifestyle, diet, and diet supplements intervention on the incidence of T2D. General overview of potential effect modifiers of lifestyle (**a**), dietary (**b**), and supplement (**c**) interventions on the incidence of type 2 diabetes. The *Y* axes indicate potential effect modifiers, and the *X* axes illustrate the total number of trial participants included in the studies investigating each modifier. The proportion of gray or white in each bar indicates the number of trial participants included in the studies where there was (gray) or was not (white) an effect by the effect modifier. Caution is warranted because whether an effect modifier did (or did not) have an effect is based on statistical significance from the publication's summary statistics. It is improbable that the effect modifier strictly did (or did not) have an effect on every participant included in that publication. The number of trials and trial participants are plotted because some trials (e.g., DPP) had multiple studies published using the same participants, so that the participant number would be heavily skewed. There was no instance where the same trial had multiple published studies evaluating the same effect modifier showing different results (e.g., there was no difference between sexes on the PREDIMED trial's effect on T2D incidence in their primary vs. subgroup studies/publications). The number at the end of each bar represents the number of trials for each potential effect modifier. *indicates an exception for genetics because the effect modifiers (SNPs or GRS) were all uniquely distinct but are presented together under the categories of "SNP" or "GRS" here.

Table 3 Efficacy of T2D preventive interventions according to clinical effect modifiers.

	T2D preventive strategies								
	Lifestyle intervention			Dietary pattern intervention			Dietary supplements intervention		
Modifier	Number of studies	Effect modification[a]	Certainty of evidence[b]	Number of studies	Effect modification[a]	Certainty of evidence[b]	Number of studies	Effect modification[a]	Certainty of evidence[b]
BMI	14	Yes: 5 studies No: 9 studies	Grade D	3	No: 3 studies	Grade D	4	Yes: 1 study No: 3 studies	Grade D
Prediabetes	18	Yes: 8 studies No: 10 studies	Grade D	1	No: 1 study	Grade D	1	No: 1 study	Grade D
Family history	3	Yes: 1 study No: 2 studies	Grade D	–	–		3	Yes: 2 studies No: 1 study	Grade D
Dyslipidemia/ medications	1	No: 1 study	Grade D	2	Yes: 2 studies	Grade D	2	Yes: 1 study No: 1 study	Grade D
Hypertension	–	–	–	2	Yes: 1 study No: 1 study	Grade D	2	No: 2 studies	Grade D
Metabolic syndrome	–	–	–	1	Yes: 1 study	Grade D	1	No: 1 study	Grade D
Menopausal status, HRT use	–	–	–	–	–	–	3	No: 3 studies	Grade D

Overview of the included studies investigating whether clinical factors modify the response to T2D preventive intervention strategies.
[a]Yes/No corresponds to significant/nonsignificant effect modification, as reported in the study.
[b]Certainty of evidence denotes consistency, Grading based on Diabetes Canada scale A to D.

Table 4 Efficacy of T2D preventive interventions according to behavioral effect modifiers.

	T2D preventive strategies								
	Lifestyle intervention			Dietary pattern intervention			Dietary supplements intervention		
Modifier	Number of studies	Effect modification[a]	Certainty of evidence[b]	Number of studies	Effect modification[a]	Certainty of evidence[b]	Number of studies	Effect modification[a]	Certainty of evidence[b]
Smoking	2	Yes: 2 studies	Grade D	1	No: 1 study	Grade D	3	No: 3 studies	Grade D
Physical activity	3	Yes: 2 studies No: 1 study	Grade D	1	No: 1 study	Grade D	3	No: 3 studies	Grade D
Alcohol intake	1	Yes: 1 study	Grade D	–	–	–	3	No: 3 studies	Grade D
Diet and supplements	–	–	–	2	No: 2 studies	Grade D	6	No: 6 studies	Grade D

Overview of the included studies investigating whether behavioral factors at baseline modify the response to T2D preventive intervention strategies.
[a]Yes/No corresponds to significant/nonsignificant effect modification, as reported in the study.
[b]Certainty of evidence denotes consistency, Grading based on Diabetes Canada scale A to D.

dietary interventions in the prevention of T2D has only low to very-low certainty (Table 5 and Fig. 2).

Grading of evidence certainty. Although our systematic review included intervention studies, most RCTs with low risk of bias, we evaluated certainty through our hypothesis of identifying valid effect modifiers to inform precision prevention. None of the studies included a priori consideration of intervention interactions with individual-level characteristics or risk factors in their study design, which were largely conducted as post hoc analyses. As a result, statistical power was often limited. Further, most did not adjust for individual-level risk factors, undermining the validity of interpreting effect modifiers' role independent of other traits. These considerations were factored into the major downgrading of the evidence (Tables 2–5).

Table 5 Efficacy of T2D preventive interventions according to molecular effect modifiers.

	T2D preventive strategies					
	Lifestyle intervention			Dietary pattern intervention		
Modifier	Number of studies	Effect modification[a]	Certainty of evidence[b]	Number of Studies	Effect modification[a]	Certainty of evidence[b]
T2D single SNPs	17	Yes: 9 studies No: 7 studies Not reported: 1 study	Grade D	1	Yes: 1 study	Grade D
Diabetes polygenic score	5	Yes: 1 study No: 4 studies	Grade D	-	-	-
Metabolites/miRNA	-	-	-	3	Yes: 3 studies	Grade D

Overview of the included studies investigating whether genetic and molecular factors at baseline modify the response to T2D preventive intervention strategies.
[a]Yes/No corresponds to significant/nonsignificant effect modification, as reported in the study.
[b]Certainty of evidence denotes consistency, Grading based on Diabetes Canada scale A to D.

Discussion

We performed a comprehensive systematic review to identify individual-level sociodemographic, clinical, behavioral, or molecular factors that could modify the efficacy of T2D prevention strategies. Overall, we find low to very low certainty of evidence that traits such as age, sex, BMI, race/ethnicity, socioeconomic status, baseline lifestyle factors, or genetics consistently and validly modify the effectiveness of lifestyle and behavioral interventions. Individuals with prediabetes at baseline benefit slightly more from prevention interventions than those without prediabetes, but the certainty of the evidence was low. This can be explained by relative and absolute risk differences among people with/without prediabetes. However, whether the modest benefit reported in these studies was due to poor health status or other correlated risk factors cannot be ascertained based on the available evidence.

Large randomized clinical trials have consistently demonstrated that a healthy lifestyle or dietary interventions can prevent or delay T2D[3,4,6,17]. However, there is large inter-individual variability in response to these preventive interventions, in which some people seem to greatly benefit from T2D preventive interventions. Precision prevention aims to identify participant characteristics that determine this variability in response to ultimately tailor preventive strategies to subgroups of individuals that are likely to benefit the most. So far, no studies exist that were prospectively designed to determine interactions by a baseline trait or factor with an intervention to prevent T2D. We evaluated the evidence base and identified several stratified post hoc analyses of existing prevention intervention trials. In post hoc analyses, the participant population is stratified by a potential effect modifier, and the efficacy of the intervention is tested within each stratum and compared across the strata, which reduces statistical power and increases type 2 error.

Furthermore, precision prevention strategies may be optimized by incorporating several individual-level factors into decision-making, whereas the current literature predominantly evaluates one stratified trait at a time. For example, correlated behaviors, such as physical activity, diet, and smoking, might provide more information when considered collectively than individually. Clinical trials specifically designed to investigate the influence of sociodemographic, clinical, behavioral, or molecular factors on the response to T2D preventive strategies are needed to generate valid and robust evidence before the implementation of T2D precision prevention strategies.

One area of promise warranting further research is the presence of prediabetes at baseline and whether this may be targeted in future precision prevention research. Low certainty evidence suggests that individuals at risk of T2D or with prediabetes at baseline benefit slightly more from prevention interventions than those not at risk of T2D[3–6]. However, the evidence is inconsistent, even though the studies report that a lifestyle intervention, compared to standard care, results in higher T2D reduction rates among studies conducted in Asia[17–20]. Beyond the methodological limitations of the available evidence, an additional reason for inconsistent evidence supporting the greater effectiveness of lifestyle interventions for the prevention of T2D among individuals with prediabetes is due to the heterogeneity that characterizes this condition. Prediabetes refers to a pathophysiological state of early alterations in glucose metabolism that precedes the development of diabetes. Still, the mechanisms by which glucose is elevated are very different and could range from those with primary alterations in insulin secretion pathways to those with primary insulin resistance[21]. Clinical trials specifically designed to capture the nuances and complexity of early glycemic alterations and whether individuals with distinct pathophysiological features benefit from more targeted preventive interventions are needed to fill the gap in current T2D precision prevention evidence.

Even though there are far more lifestyle intervention trials for the prevention of T2D than diet alone and diet supplementation trials, collectively, however, results for effect modification by any one factor are sparsely reported or arising from an evidence base of very different trials and patient populations. Further, many secondary analyses in this systematic review are derived from two single clinical interventions viz, the DPP and the DPS. Findings from available evidence contrast with recent clinical studies documenting variable responses to identical foods, diets, or lifestyle interventions based on inter-individual differences in demographic, clinical, genetic, gut microbiota, and lifestyle characteristics[22–24]. While these studies offer insights into variable postprandial metabolic response, their short follow-up periods, the lack of time-series data and changes in parameters that could influence response to interventions, and the inclusion of relatively young and healthy individuals preclude the generalizability to T2D prevention efforts. Whether the promise of T2D precision prevention is matched by evidence of the long-term beneficial impact remains uncertain. Still, interest and activity in this field are proliferating to identify factors underlying variable nutritional responses and develop algorithms to predict individual responses to nutrients, foods, and dietary patterns.

While recent studies support the benefits of losing body weight loss on the risk of developing T2D regardless of the mechanisms underlying T2D, there is still enormous variability in individual response to weight-loss interventions. For example, the DIETFITS study[25], showed that weight change varied widely within

each study group, ranging from a loss of ~30 kg to a gain of ~10 kg. While weight loss is critical in T2D prevention, these findings reinforce the continued effort to identify molecular, environmental and social characteristics underlying the variable response to diabetes prevention interventions.

Our systematic review had some limitations. The scope of our literature review as part of the PDMI was broad and inclusive of diverse study designs, T2D prevention strategies, study populations, and effect modification analyses. Although this resulted in a heterogeneous evidence base and did not provide an opportunity for meta-analysis, we qualitatively synthesized the evidence for precision prevention. Our hypothesis originally spanned to include observational studies, which were ultimately excluded due to the uncertainty of their being readily related to clinical interventions. Protocol amendments were registered to reflect these decisions prior to study screening and extraction. Moreover, as our scope only included moderators of the intervention efficacy on T2D, which are typically measured prior to or at baseline[26], important mediators of the intervention effects on T2D as e.g., weight loss was not addressed and discussed. This will be important to address in future studies to gain a deeper understanding of heterogenous lifestyle interventions responses.

In conclusion, our systematic review and synthesis of the T2D prevention literature provide low to very low certainty evidence that sociodemographic, clinical, lifestyle, or molecular factors are more useful, valid, and consistent in informing T2D precision prevention strategies than current interventions. We also uncover several areas of potential for growth in the precision medicine field, including prospectively designed interventions and clinical trials incorporating the investigation of treatment response heterogeneity.

Data availability

This systematic review compiles data available in clinical studies. The PMIDs of included studies are available in Table 1. The study-specific numeric estimates for the effect modification has been given in Supplementary Data 1. The source data for Fig. 2 is provided in Supplementary Data 2. All other extracted data have been summarized in the figures and tables presented in the manuscript and are available from the corresponding author on reasonable request.

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Competing interests

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