Diabetes Ther
https://doi.org/10.1007/s13300-023-01455-9

COMMENTARY

A Systematic Approach to Treating Early Metabolic Disease and Prediabetes

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Received: June 30, 2023 / Accepted: July 19, 2023

ABSTRACT

At least 70% of US adults have metabolic disease. However, less is done to address early disease (e.g., overweight, obesity, prediabetes) versus advanced disease (e.g., type 2 diabetes mellitus, coronary artery disease). Given the burden of advanced metabolic disease and the burgeoning pandemics of obesity and prediabetes a systematic response is required. To accomplish this, we offer several recommendations: (A) Patients with overweight, obesity, and/or prediabetes must be consistently diagnosed with these conditions in medical records to enable population health initiatives. (B) Patients with early metabolic disease should be offered in-person or virtual lifestyle interventions commensurate with the findings of the Diabetes Prevention Program. (C) Patients unable to participate in or otherwise failing lifestyle intervention must be screened to assess if they require pharmacotherapy. (D) Patients not indicated for, refusing, or failing pharmacotherapy must be screened to assess if they need bariatric surgery. (E) Regardless of treatment approach or lack of treatment, patients must be consistently screened for the progression of early metabolic disease to advanced disease to enable early control. Progression of metabolic disease from an overweight yet otherwise healthy person includes the development of prediabetes, obesity ± prediabetes, dyslipidemia, hypertension, type 2 diabetes, chronic kidney disease, coronary artery disease, and heart failure. Systematic approaches in health systems must be deployed with clear protocols and supported by streamlined technologies to manage their population's metabolic health from early through advanced metabolic disease. Additional research is needed to identify and validate optimal system-level interventions. Future research needs to identify strategies to roll out systematic interventions for the treatment of early metabolic disease and

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Published online: 05 August 2023

to improve the metabolic health among the progressively younger patients being impacted by obesity and diabetes.

Keywords: Diabetes; Obesity; Overweight; Population health; Prediabetes; Prevention

Key Summary Points
Diabetes and other metabolic diseases are highly undesirable.
Prediabetes and obesity should be consistently diagnosed to facilitate population health initiates.
With patient-specific factors considered, evidence supports treating prediabetes and obesity with lifestyle intervention, medications, and bariatric surgery.
Systematic approaches to preventing or delaying the progression of metabolic disease are needed, given the pandemics of obesity and prediabetes.
Additional research is needed to identify the best ways to roll out interventions to treat early metabolic disease.
Additional research is needed to improve interventions targeting the metabolic health of youths.

A speaker asked for hands to be raised in an auditorium where there were more held doctorate degrees than people and the average body mass index (BMI) likely approximated 22 kg/m^2. "If you'd like to participate, please raise your hand if you do not have type 2 diabetes." Many hands went up. Then the speaker asked, "please keep your hand in the air if you are indifferent to whether or not you develop type 2 diabetes." No hands remained in the air. Next, the speaker asked, "please raise your hand if you address new-onset type 2 diabetes in clinic." Many hands went up. Then the speaker asked, "please keep your hand in the air if you have seen a baseline glycated hemoglobin of at least 8%." No hands went down. "How about 9%?" No hands went down. "What about 10%?" Still, no hands went down. "Ok, 11%?" The hands of a few of the younger clinicians went down. Not until 14% were only a few hands remaining. When this exercise is repeated, the results are invariable. No one wants to develop type 2 diabetes, and many patients present for care after type 2 diabetes has had the opportunity to cause irreparable damage to life [1], limb [2], and a bank account [3].

Why, then does the American Diabetes Association write, "[p]rediabetes should not be viewed as a clinical entity in its own right but rather as a risk factor for progression to diabetes and cardiovascular disease" [4]? How is this different from hypertension, which daily causes no symptoms, but rather is a risk factor for myocardial infarction, stroke, and heart failure [5]? Why, as a health system, are we not doing more to treat overweight, obesity, and prediabetes? There appears to be a disconnect between clinician preference for their health, their interpretation of the evidence, and their approach to patient care. This commentary will reconcile this disconnect and propose a way forward. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

THE STATE OF THINGS

At least 70% of United States (US) adults have metabolic disease (e.g., overweight, obesity, hypertension, prediabetes, diabetes, coronary artery disease), including over 100 million US adults with prediabetes [5]. There is debate among guidelines and nations regarding what should be indicative of prediabetes; however, it is somewhat trivial as it does not impact the primary patient care approach. Whether a patient has overweight, obesity, or prediabetes (either defined as a fasting blood glucose of 100 mg/dL or 110 mg/dL), they would benefit from improvements in their diet and exercise habits, as would all patients with metabolic disease [6].

Disagreement becomes meaningful in choosing pharmacotherapy. The American Diabetes Association reserves medication therapy, specifically metformin, for patients with higher degrees of dysglycemia [6]. Metformin is recommended to prevent type 2 diabetes in adults aged 25–59 years, with BMI $\geq$ 35 kg/m^2, fasting glucose $\geq$ 110 mg/dL, glycated hemoglobin $\geq$ 6.0%, and in women with prior gestational diabetes [6]. The American Association of Clinical Endocrinology does not require a higher degree of dysglycemia for medication therapy (i.e., metformin, pioglitazone, acarbose) and further recommends glucagon-like peptide 1 (GLP-1) receptor agonists or phentermine/topiramate extended-release among patients with prediabetes also indicated for weight loss pharmacotherapy (obesity or BMI $\geq$ 27 kg/m^2 with weight-related comorbidity) [7]. Conversely, others have advocated for no pharmacotherapy for prediabetes [8–10]. Indeed a state-of-the-art review from the *Journal of the American College of Cardiology* concluded, "[w]ith regard to primary prevention of [cardiovascular disease], it is clear that for [diabetes mellitus]… there is no role for pharmacological interventions in individuals without overt disease." But was this clear then, and if so, is it still now?

HARD OUTCOMES AND THE DIABETES PREVENTION PROGRAM

Improving lifestyle, noted by healthier diet and more exercise, is the core approach to preventing new-onset type 2 diabetes [6]. Notable goals and approaches to intensive lifestyle intervention include achieving and maintaining a 7% reduction in baseline body weight through moderate-intensity exercise ($\geq$ 150 min/week) and a healthy reduced-calorie diet (500–-1000 kcal per day below the amount needed to maintain body weight) [6]. While the Diabetes Prevention Program focused diet change on reducing total dietary fat and calories, several patient-tailored approaches to diet can be used for diabetes prevention including Mediterranean-style, low-carbohydrate, vegetarian, plant-based, and Dietary Approaches to Stop Hypertension (DASH).

The Diabetes Prevention Program demonstrated the impact of intensive lifestyle intervention in preventing new-onset type 2 diabetes [11]. As such, the trial offered a group-implemented lifestyle intervention to all participants after the 3-year initial study of intensive lifestyle intervention, metformin, and placebo [12]. Yet, even at 21 years of follow-up, both metformin and intensive lifestyle intervention resulted in significantly fewer cases of new-onset type 2 diabetes versus placebo (placebo 60%, metformin 55%, lifestyle intervention 53%, $p < 0.01$ for both interventions versus placebo) [13]. Several important points can be gleaned from these data.

First, an absolute reduction of 5–7% over 21 years in new-onset type 2 diabetes is not dramatic [13]. Second, with the small difference in the development of type 2 diabetes overall, it is not surprising that the study did not demonstrate a difference in microvascular or macrovascular outcomes between treatment groups [13, 14]. Third, the smaller absolute difference is less surprising as all participants were offered a group lifestyle intervention following year 3. Fourth, the lifetime risk of developing new-onset type 2 diabetes is high among adults with prediabetes, even in a controlled trial with optimized care. In addition to the findings by treatment assignment, overall findings demonstrated significant benefit from *not developing* versus *developing* type 2 diabetes in the long-term follow-up. At 15 years, not having diabetes was associated with a 28% lower prevalence of microvascular complications [14]. Additionally, at an average follow-up of 22 years, not having diabetes was associated with a 57% lower risk of early eye changes, a 37% lower risk of kidney disease, and a 39% lower risk of major cardiovascular disease endpoints [15].

A clinical treatment approach either values preventing type 2 diabetes or it does not. Clinicians cannot abdicate the decision with a patient in front of them. No decision to promote metabolic health is a decision not to promote metabolic health. So, each clinician must answer whether attempting to prevent type 2 diabetes helps. The evidence suggests it

does. Importantly, there is no economic rationale for withholding lifestyle intervention or metformin as both are cost-saving in attempting to prevent of type 2 diabetes [16–18]. A key point in the preceding sentence is the word "attempting" as adherence significantly waned over time in the group assigned to receive metformin [13]. Even so, diabetes prevalence remained lower with metformin, and cost-savings were achieved [12, 16, 17]. Therefore, even if the evidence suggesting a macro- and microvascular benefit from not developing type 2 diabetes is discounted, the primary interventions to delay or prevent new-onset type 2 diabetes are cost-saving, with the added benefit of avoiding type 2 diabetes in some patients as highlighted above. Indeed, as illustrated above and in the literature, type 2 diabetes impacts a range of patient-centered outcomes [19]. Thus, lifestyle intervention and metformin should be deployed systematically to improve patient outcomes and reduce healthcare spending.

In addition to the overall benefits observed in the Diabetes Prevention Program, five key points further highlight the expected benefit of metformin for diabetes prevention in practice. First, the benefit of metformin in preventing type 2 diabetes is not simply masking type 2 diabetes. The majority of metformin's benefit was retained following metformin washout in the Diabetes Prevention Program [20]. Second, it is established that greater adherence to metformin improved its effect on reduced new-onset type 2 diabetes [21]. Thus, patients choosing and staying on metformin can expect benefits beyond those observed in the Diabetes Prevention Program. Third, it is established that a major health disparity exists in diabetes prevalence [22, 23]. Diabetes prevention efforts must account for health disparity and access to care [22]. Not all patients have access to healthy foods or intensive lifestyle interventions. As such, patients should be offered metformin when indicated as the "in practice" alternative to metformin for some patients would be no intervention, far below the level of care provided to patients in the placebo group of the Diabetes Prevention Program. Fourth, key subgroups benefited from metformin more or less in the Diabetes Prevention Program. These subgroups are mirrored in the American Diabetes Association's recommendations [6]. Thus, targeting metformin therapy in practice toward patients younger and more obese would generate a benefit greater than that observed in the Diabetes Prevention Program as obesity is a trigger for increasing insulin resistance and subsequent new-onset type 2 diabetes [24]. Fifth, men, particularly younger men, are underrepresented among those participating in the National Diabetes Prevention Program [25]. In the Diabetes Prevention Program, men experienced a reduction in coronary artery calcium with metformin therapy [26]. Thus, the patients least likely to participate in intensive lifestyle interventions (i.e., younger patients and men) are also the most likely to benefit from metformin.

A WAY FORWARD

Overweight, obesity, and prediabetes must be diagnosed for two key reasons. First, this enables population health approaches to improve patient care and outcomes [27]. With a diagnosis, these efforts can be done efficiently. Population health studies in hypertension and diabetes have demonstrated improvements in care, and patient identification is simplified when International Classification of Diseases (ICD) codes can be searched electronically [28, 29]. Without a diagnosis, population health initiatives become less efficient if they must start with screening [30, 31]. Specific to prediabetes, when patients are already screened for type 2 diabetes in practice, the return on investment of screening is diminished when prediabetes is identified… but not diagnosed [31]. Second, patients receiving a diagnosis should receive a plan in a progress note for the new problem identified as standard care. Indeed, it has been demonstrated that diagnosed obesity prompts action by clinicians [32]. However, many patients with prediabetes receive no diagnosis and no intervention [33]. Regardless of intervention, the diagnosis of overweight, obesity, or prediabetes can be done at no added cost (as screening is already being

done) and can improve the process for continued screening for progression to overt metabolic disease, including type 2 diabetes. By formalizing a follow-up plan for subsequent screening, it may be possible to limit patients being lost to follow-up and later presenting with significant glucose elevations as their new baseline or other advanced metabolic disease.

Recommendations for screening for prediabetes and type 2 diabetes have been established by multiple guidelines [4, 6, 34]. Patients lost to follow-up with prediabetes who later present with type 2 diabetes and significantly elevated glucose appear to be at substantially higher risk for complications [35–37]. Conversely, patients benefit from the early treatment and control of type 2 diabetes [35, 38, 39]. Moreover, the benefit of early treatment and control of type 2 diabetes is likely underestimated as newer medications for the treatment of type 2 diabetes significantly reduce cardiovascular events [40–44]. Given the benefit of early treatment and control of type 2 diabetes [35], and the harm associated with developing type 2 diabetes versus not developing type 2 diabetes [14, 15], we propose it is appropriate for clinicians to operate with the understanding that patients significantly benefit when they do not develop type 2 diabetes. Among various populations, the interventions which appear to have the clearest data regarding diabetes prevention and cardiovascular benefit are intensive lifestyle intervention [11, 15, 16, 45], metformin [11, 12, 20, 35, 46], pioglitazone [47, 48], and liraglutide and semaglutide [40–42, 49, 50]. As such, we propose these interventions should be systematically deployed as supported by evidence and guideline for the prevention of type 2 diabetes [6, 7, 34].

Patients with the early metabolic disease (e.g., overweight) are at notable risk for the continued progression of their metabolic disease, including obesity ± prediabetes, dyslipidemia, hypertension, chronic kidney disease, coronary artery disease, heart failure, and death [4, 51–55]. Therefore, as population health initiatives across health systems seek to improve care quality, prediabetes should be incorporated into overall metabolic health for two reasons. First, it is presently undertreated and a necessary component of comprehensive metabolic care. Second, it is an early diagnosis of metabolic disease in addition to overweight and obesity. By identifying prediabetes, there is a greater chance to intervene to slow metabolic disease progression overall. Particularly in younger patients, treating overweight, obesity, and prediabetes earlier and more aggressively has to potential to support healthier aging. Moreover, employer-based health insurance tends to have better prescription drug coverage versus Medicare, thus potentially enabling greater access to novel medications and treatments with greater effects in working-age patients.

MORE IS NEEDED

Greater action is needed to systematically deploy interventions known to be effective in treating overweight, obesity, and prediabetes. Two key approaches include health system protocol and electronic health record decision information support [56]. Health system protocol is needed to prompt clinician behavior. No medication has a specific US Food and Drug Administration-approved indication for prediabetes, though medications are approved for obesity and overweight (BMI $\geq$ 27 kg/m^2 with weight-related comorbidity). However, evidence and guideline strongly support "off-label" use for prediabetes. As such, health systems must enact protocols to encourage evidence-based treatments and destigmatize off-label pharmacotherapy for prediabetes in addition to streamlining the appropriate use of medications for weight loss and standardize referrals to bariatric surgery. Decision information support can facilitate these efforts by promoting the consistent diagnosis of overweight, obesity, and prediabetes. Moreover, it can be paired with one-click referral to community lifestyle interventions partnered with the National Diabetes Prevention Program. It is in these programs where patients can receive the education and support needed to adopt healthy patterns of diet and exercise [25]. Additionally, based on predetermined parameters, decision information support can identify patients that may be

indicated for pharmacologic or surgical treatment.

The health system approaches outlined above can be implemented broadly today. Research is needed to refine replicable methods to deploy these interventions. However, the 20-plus-year trends in obesity and diabetes suggest systemic factors negatively impacting metabolic health [57–59]. One analysis identified Sugar Research Foundation sponsored research as problematic [60], the timing of which roughly corresponded to the start of the increasing prevalence of obesity and diabetes [57–59]. Now many commonly purchased food items contain added sugars [61, 62], a known risk factor for cardiovascular disease mortality [63]. The food supply must be examined and addressed to enable healthy choices, without the economic burden of "organic" items which are also less accessible [64–66]. Through public health approaches to improve the food supply it may be possible to improve the metabolic health of whole populations by addressing excess (and empty) calories [67], insufficient vitamin D [68], insufficient dietary fiber [69], and insufficient healthy proteins [70].

The need to address metabolic health systematically is urgent. While some cling to BMI as inaccurate with the hope that the metabolic health of the USA is better than as measured by BMI, recent data indicate that, if anything, BMI underidentifies people with obesity and that the metabolic health of the USA is even worse than BMI would suggest [71, 72]. And today, poor metabolic health impacts younger adults, adolescents, and children more than ever [73–76]. Indeed, the number of children developing and maintaining an unhealthy lifestyle portends an insurmountable wave of metabolic disease [74–76]. Recent evidence suggests the trend of increased new pediatric type 2 diabetes is not reversing post-pandemic [77]. Moreover, body image, depression, social media, gaming, screen time, parental role, school role, and socioeconomic status complicate reaching and positively impacting children and adolescents [73, 78, 79], those most likely to benefit long-term from adopting and maintaining a healthy lifestyle. Therefore, we propose research needs with the potential to improve the metabolic health of youth without compromising, and hopefully improving, mental health.

What is the Best Way to Start Conversations with Children, Adolescents, and Parents About Metabolic Health?

It is quite possible, and even likely, that the answer to this question will vary by age, sex, culture, and socioeconomic status. Additionally, we expect various individuals to be able to positively impact a child or adolescent's life and metabolic health, though each may need a different conversation starter. Parents and guardians are a vital influence in a child's life and need to be equipped to address health with their child in a positive way. Other key childhood points of contact include teachers, pediatricians, and dentists. The start of conversations regarding metabolic health in all circumstances is vital to promote healthy change in lifestyle, while being cognizant of mental health issues, body image/self-esteem issues, and identity. We hypothesize empowerment and a focus on wellness will be important in broadly supporting physical and mental health. Regarding parents, particularly the parents of students who are elementary-age or younger, research is needed on how to deliver nutrition and physical activity education to parents and prompt parents to impose healthy dietary and physical activity habits on their children in an appropriate way.

What is the Best Way to Systematically Increase Physical Activity Among Public School Attendees?

Lifestyle interventions focusing on improving eating and physical activity behaviors have become standard approaches to improving health, although generally yielding only modest impact [80]. Unfortunately, sweat, stigma, fitting in, time, and comparison may jeopardize consistent participation in physical activity among various groups [81–83]. Moreover, training among school teachers in physical activity, if any, is not standardized [84–86]. Limited time, resources for exercise, space, and

personnel appear to be obstacles [81, 82]. We hypothesize these obstacles can be overcome using current school resources and personnel through additional targeted pieces of training for school teachers, protocolized in-class physical activity curriculum, and directing teachers to prioritize physical activity time [84, 85].

What is the Best Way to Combat Social Media, Screen Time, and Gaming Among Children and Adolescents?

There appears to be a link between social media and depression [78, 87]. A bidirectional relationship between obesity and depression is known [79, 88]. Limited data suggest video game time impairs physical health, having an impact on total sedentary time [89]. As time has been established as a key limiting factor in physical activity, we pose time spent playing video games as an important factor in potentially limiting physical activity time. Indeed, digital addiction has become a major problem exacerbated by the pandemic [90]. Youth have long been known to be particularly susceptible to addiction based on neurodevelopment [91], and screen time, social media, and gaming appear to impact the same dopamine reward pathway as opioids [92, 93]. Together, there appears to be a great but ill-defined harm associated with screens in all forms, with a progressively worse impact as use increases and age decreases, at the very least by promoting increased sedentary time. More research is needed to clarify this harm and support children and parents in methods to avoid this harm.

A CALL TO ACTION

Systematic approaches to promote metabolic health are available but must be deployed including the use of health system protocols and technological approaches to streamline metabolic care in an already burdened health system [94]. However, these approaches are limited to the extent they are an institutional priority. Smaller physician groups may not have an information systems team able to deploy decision information support. Additionally, depending on the physician group's business structure, there may not be a medical officer or therapeutics committee able to enact and monitor protocols. Even in larger health systems, approving protocols and building out the needed support in electronic health records can be a long process. Thus, institutional commitment and incentive from insurers are needed. A 1-year time horizon for quality metrics and shared savings is not likely to capture the benefit of systematically treating early metabolic disease. Thus, research, streamlined and replicable systems, and updated policy are needed to optimize a systematic approach to treating early metabolic disease, its institutional rollout, and its incentivization.

The systematic treatment of early metabolic disease must include support for adopting a healthy diet and regular exercise in addition to the judicious, but systematic, use of medications and surgery [6, 45, 95]. While evidence supports lifestyle intervention, medications, and surgery, again more research is needed. Specifically, research is needed to identify the best way to get patients engaged in and adherent to a lifestyle intervention program. Similarly, research is needed to identify the best way to identify and approach patients suitable for metformin or other medication therapy for early metabolic disease. Unfortunately, newer medications are expensive and approaches to increase patient access without overwhelming the healthcare system need to be developed. As part of this, the impact of higher-dose GLP-1 receptor agonists on cardiovascular outcomes needs to be assessed in addition to assessing their cardiovascular outcomes in patients without type 2 diabetes. A Study of Tirzepatide on the Reduction on Morbidity and Mortality in Adults with Obesity (SURMOUNT-MMO) will help shed light on this as it plans to enroll 15,000 patients without diabetes and will assess the composite outcome of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and heart failure events [96].

Lifestyle diseases require a lifetime of action. Indeed, the impact of metabolic disease on human health begins prior to conception, as the metabolic health of mothers impacts their

offspring [97]. The impact of obesity and diabetes globally has escalated over the past 20 years and the projections are ominous as obesity is expected to drive the global prevalence of diabetes to 1.3 billion by 2050 [98]. While food supply and societal factors need to be improved, patients cannot wait. Continuing the approach of diet and exercise only for metabolic health is not patient-centered, promotes health disparity, and is illogical as it has failed for over 20 years [22, 23, 57–59].

ACKNOWLEDGEMENTS

Author Contribution. Nicholas W. Carris wrote the first draft. All named authors reviewed the manuscript critically for important intellectual content, approved the submitted version, and agree to be accountable for the work.

Funding. No funding or sponsorship was received for this study or publication of this article.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Conflict of Interest. Christopher DuCoin declares consulting for Johnson & Johnson, Medtronic, and Intuitive. Nicholas Carris, Brian Bunnell, Rahul Mhaskar, and Marilyn Stern have nothing to disclose.

REFERENCES

1. Raghavan S, Vassy JL, Ho YL, et al. Diabetes mellitus-related all-cause and cardiovascular mortality in a national cohort of adults. J Am Heart Assoc. 2019;8: e011295. https://doi.org/10.1161/jaha.118.011295.

2. Lin C, Liu J, Sun H. Risk factors for lower extremity amputation in patients with diabetic foot ulcers: a meta-analysis. PLoS ONE. 2020;15:e0239236. https://doi.org/10.1371/journal.pone.0239236.

3. Gao CC, Espinoza Suarez NR, Toloza FJK, et al. Patients' perspective about the cost of diabetes management: an analysis of online health communities. Mayo Clin Proc Innov Qual Outcomes. 2021;5:898–906. https://doi.org/10.1016/j.mayocpiqo.2021.07.003.

4. ElSayed NA, Aleppo G, Aroda VR, et al. 2. Classification and diagnosis of diabetes: standards of care in diabetes-2023. Diabetes Care. 2023;46:S19–40. https://doi.org/10.2337/dc23-S002.

5. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2023 update: a report from the American Heart Association. Circulation. 2023;147:e93–621. https://doi.org/10.1161/cir.0000000000001123.

6. ElSayed NA, Aleppo G, Aroda VR, et al. 3. Prevention or delay of type 2 diabetes and associated comorbidities: standards of care in diabetes-2023. Diabetes Care. 2023;46:S41–8. https://doi.org/10.2337/dc23-S003.

7. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: comprehensive type 2 diabetes management algorithm - 2023 update. Endocr Pract. 2023;29:305–40. https://doi.org/10.1016/j.eprac.2023.02.001.

8. Redberg RF. The medicalization of common conditions. JAMA Intern Med. 2016;176:1863. https://doi.org/10.1001/jamainternmed.2016.6210.

9. Shahraz S, Pittas AG, Kent DM. Prediabetes risk in adult Americans according to a risk test. JAMA Intern Med. 2016;176:1861–3. https://doi.org/10.1001/jamainternmed.2016.5919.

10. Farr OM, Mantzoros CS. Treating prediabetes in the obese: are GLP-1 analogues the answer? Lancet. 2017;389:1371–2. https://doi.org/10.1016/s0140-6736(17)30315-x.

11. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403. https://doi.org/10.1056/NEJMoa012512.

12. Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet. 2009;374:1677–86. https://doi.org/10.1016/s0140-6736(09)61457-4.

13. Goldberg RB, Orchard TJ, Crandall JP, et al. Effects of long-term metformin and lifestyle interventions on cardiovascular events in the diabetes prevention program and its outcome study. Circulation. 2022;145:1632–41. https://doi.org/10.1161/circulationaha.121.056756.

14. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol. 2015;3:866–75. https://doi.org/10.1016/s2213-8587(15)00291-0.

15. American Diabetes Association. New data from diabetes prevention program outcomes study shows persistent reduction of type 2 diabetes development over 22-year average follow-up. https://diabetes.org/newsroom/press-releases/2020/new-data-from-diabetes-prevention-program-outcomes-study-shows-persistent-reduction-of-t2d-development-over-22-year-average-follow-up. Accessed 14 Jun 2023.

16. Herman WHES, Ratner RE, Montez MG, et al. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. Diabetes Care. 2012;35:723–30. https://doi.org/10.2337/dc11-1468.

17. Carris NW, Cheng F, Kelly WN. The changing cost to prevent diabetes: a retrospective analysis of the Diabetes Prevention Program. J Am Pharm Assoc. 2003;2017(57):717–22. https://doi.org/10.1016/j.japh.2017.05.015.

18. Centers for Medicare and Medicaid Services. Medicare Diabetes Prevention Program expansion. https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2016-Fact-sheets-items/2016-07-07.html. Accessed 21 Jun 2018.

19. Nano J, Carinci F, Okunade O, et al. A standard set of person-centred outcomes for diabetes mellitus: results of an international and unified approach. Diabet Med. 2020;37:2009–18. https://doi.org/10.1111/dme.14286.

20. Diabetes Prevention Program Research Group. Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. Diabetes Care. 2003;26:977–80. https://doi.org/10.2337/diacare.26.4.977.

21. Walker EA, Gonzalez JS, Tripputi MT, et al. Long-term metformin adherence in the Diabetes Prevention Program Outcomes Study. BMJ Open Diabetes Res Care. 2020. https://doi.org/10.1136/bmjdrc-2020-001537.

22. Spencer-Bonilla G, Rodriguez-Gutierrez R, Montori VM. What we don't talk about when we talk about preventing type 2 diabetes-addressing socioeconomic disadvantage. JAMA Intern Med. 2016;176:1053–4. https://doi.org/10.1001/jamainternmed.2016.2952.

23. Gaskin DJ, Thorpe RJ Jr, McGinty EE, et al. Disparities in diabetes: the nexus of race, poverty, and place. Am J Public Health. 2014;104:2147–55. https://doi.org/10.2105/ajph.2013.301420.

24. Wondmkun YT. Obesity, insulin resistance, and type 2 diabetes: associations and therapeutic implications. Diabetes Metab Syndr Obes. 2020;13:3611–6. https://doi.org/10.2147/dmso.S275898.

25. Ely EK, Gruss SM, Luman ET, et al. A national effort to prevent type 2 diabetes: participant-level evaluation of CDC's National Diabetes Prevention Program. Diabetes Care. 2017. https://doi.org/10.2337/dc16-2099.

26. Goldberg RB, Aroda VR, Bluemke DA, et al. Effect of long-term metformin and lifestyle in the diabetes prevention program and its outcome study on coronary artery calcium. Circulation. 2017. https://doi.org/10.1161/circulationaha.116.025483.

27. Williams J, Sachdev N, Kirley K, et al. Implementation of diabetes prevention in health care organizations: best practice recommendations. Popul Health Manag. 2022;25:31–8. https://doi.org/10.1089/pop.2021.0044.

28. Dugdale DC, Khor S, Liao JM, Flum DR. Association between a population health intervention and hypertension control. J Gen Intern Med. 2022;37:4095–102. https://doi.org/10.1007/s11606-022-07522-4.

29. Tanumihardjo JP, Kuther S, Wan W, et al. New frontiers in diabetes care: quality improvement study of a population health team in rural critical access hospitals. J Gen Intern Med. 2023;38:56–64. https://doi.org/10.1007/s11606-022-07928-0.

30. Hoerger TJ, Hicks KA, Sorensen SW, et al. Cost-effectiveness of screening for pre-diabetes among overweight and obese US adults. Diabetes Care. 2007;30:2874–9. https://doi.org/10.2337/dc07-0885.

31. Chatterjee R, Narayan KM, Lipscomb J, et al. Screening for diabetes and prediabetes should be cost-saving in patients at high risk. Diabetes Care. 2013;36:1981–7. https://doi.org/10.2337/dc12-1752.

32. Banerjee ES, Gambler A, Fogleman C. Adding obesity to the problem list increases the rate of providers addressing obesity. Fam Med. 2013;45:629–33.

33. Mainous AG 3rd, Tanner RJ, Baker R. Prediabetes diagnosis and treatment in primary care. J Am Board Fam Med. 2016;29:283–5. https://doi.org/10.3122/jabfm.2016.02.150252.

34. Davidson KW, Barry MJ, Mangione CM, et al. Screening for prediabetes and type 2 diabetes: US preventive services task force recommendation statement. JAMA. 2021;326:736–43. https://doi.org/10.1001/jama.2021.12531.

35. Svensson E, Baggesen LM, Johnsen SP, et al. Early glycemic control and magnitude of HbA1c reduction predict cardiovascular events and mortality: population-based cohort study of 24,752 metformin initiators. Diabetes Care. 2017;40:800–7. https://doi.org/10.2337/dc16-2271.

36. Giraldez RR, Clare RM, Lopes RD, et al. Prevalence and clinical outcomes of undiagnosed diabetes mellitus and prediabetes among patients with high-risk non-ST-segment elevation acute coronary syndrome. Am Heart J. 2013;165:918–925.e912. https://doi.org/10.1016/j.ahj.2013.01.005.

37. Roberts RO, Kantarci K, Geda YE, et al. Untreated type 2 diabetes and its complications are associated with subcortical infarctions. Diabetes Care. 2011;34:184–6. https://doi.org/10.2337/dc10-0602.

38. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–89. https://doi.org/10.1056/NEJMoa0806470.

39. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet. 1998;352:854–65.

40. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–44. https://doi.org/10.1056/NEJMoa1607141.

41. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394:121–30. https://doi.org/10.1016/s0140-6736(19)31149-3.

42. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–22. https://doi.org/10.1056/NEJMoa1603827.

43. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28. https://doi.org/10.1056/NEJMoa1504720.

44. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–57. https://doi.org/10.1056/NEJMoa1611925.

45. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129:S102–138. https://doi.org/10.1161/01.cir.0000437739.71477.ee.

46. Han Y, Xie H, Liu Y, Gao P, Yang X, Shen Z. Effect of metformin on all-cause and cardiovascular mortality in patients with coronary artery diseases: a systematic review and an updated meta-analysis. Cardiovasc Diabetol. 2019;18:96. https://doi.org/10.1186/s12933-019-0900-7.

47. DeFronzo RA, Tripathy D, Schwenke DC, et al. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med. 2011;364:1104–15. https://doi.org/10.1056/NEJMoa1010949.

48. Kernan WN, Viscoli CM, Furie KL, et al. Pioglitazone after ischemic stroke or transient ischemic attack. N Engl J Med. 2016. https://doi.org/10.1056/NEJMoa1506930.

49. le Roux CW, Astrup A, Fujioka K, et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial.

Lancet. 2017;389:1399–409. https://doi.org/10.1016/s0140-6736(17)30069-7.

50. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021. https://doi.org/10.1056/NEJMoa2032183.

51. Cefalu WT, Buse JB, Tuomilehto J, et al. Update and next steps for real-world translation of interventions for type 2 diabetes prevention: reflections from a diabetes care editors' expert forum. Diabetes Care. 2016;39:1186–201. https://doi.org/10.2337/dc16-0873.

52. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012;379:2279–90. https://doi.org/10.1016/s0140-6736(12)60283-9.

53. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988–2014. Lancet Diabetes Endocrinol. 2018. https://doi.org/10.1016/s2213-8587(18)30027-5.

54. Cai X, Zhang Y, Li M, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. BMJ. 2020;370: m2297. https://doi.org/10.1136/bmj.m2297.

55. Cai X, Liu X, Sun L, et al. Prediabetes and the risk of heart failure: a meta-analysis. Diabetes Obes Metab. 2021;23:1746–53. https://doi.org/10.1111/dom.14388.

56. Carris NW, Corvin JA. Prediabetes: an undiagnosed pandemic. Endocr Pract. 2022;28:231–2. https://doi.org/10.1016/j.eprac.2021.10.004.

57. Ellison-Barnes A, Johnson S, Gudzune K. Trends in obesity prevalence among adults aged 18 through 25 years, 1976–2018. JAMA. 2021;326:2073–4. https://doi.org/10.1001/jama.2021.16685.

58. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. NCHS Data Brief, no 360. Hyattsville, MD: National Center for Health Statistics. 2020.

59. Centers for Disease Control and Prevention. National Diabetes Statistics Report website. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed 28 Jun 2023.

60. Kearns CE, Schmidt LA, Glantz SA. Sugar industry and coronary heart disease research: a historical analysis of internal industry documents. JAMA Intern Med. 2016;176:1680–5. https://doi.org/10.1001/jamainternmed.2016.5394.

61. Drewnowski A, Rehm CD. Consumption of added sugars among US children and adults by food purchase location and food source. Am J Clin Nutr. 2014;100:901–7. https://doi.org/10.3945/ajcn.114.089458.

62. Acton RB, Vanderlee L, Hobin EP, Hammond D. Added sugar in the packaged foods and beverages available at a major Canadian retailer in 2015: a descriptive analysis. CMAJ Open. 2017;5:E1–E6. https://doi.org/10.9778/cmajo.20160076.

63. Yang Q, Zhang Z, Gregg EW, Flanders WD, Merritt R, Hu FB. Added sugar intake and cardiovascular diseases mortality among US adults. JAMA Intern Med. 2014;174:516–24. https://doi.org/10.1001/jamainternmed.2013.13563.

64. Li C, Ghiasi A, Li X, Chi G. Sociodemographics and access to organic and local food: a case study of New Orleans Louisiana. Cities. 2018;79:141–50. https://doi.org/10.1016/j.cities.2018.03.003.

65. Sansom G, Hannibal B. Disparate access to nutritional food; place, race and equity in the United States. BMC Nutr. 2021;7:29. https://doi.org/10.1186/s40795-021-00434-2.

66. Gundala RR, Singh A. What motivates consumers to buy organic foods? Results of an empirical study in the United States. PLoS ONE. 2021;16: e0257288. https://doi.org/10.1371/journal.pone.0257288.

67. Zeng BT, Pan HQ, Li FD, Ye ZY, Liu Y, Du JW. Comparative efficacy of different eating patterns in the management of type 2 diabetes and prediabetes: an arm-based Bayesian network meta-analysis. J Diabetes Investig. 2023;14:263–88. https://doi.org/10.1111/jdi.13935.

68. Zhang Y, Tan H, Tang J, et al. Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes: a systematic review and meta-analysis. Diabetes Care. 2020;43:1650–8. https://doi.org/10.2337/dc19-1708.

69. Reynolds AN, Akerman AP, Mann J. Dietary fibre and whole grains in diabetes management: systematic review and meta-analyses. PLoS Med. 2020;17:e1003053. https://doi.org/10.1371/journal.pmed.1003053.

70. Hansen TT, Astrup A, Sjödin A. Are dietary proteins the key to successful body weight management? A systematic review and meta-analysis of studies assessing body weight outcomes after interventions with increased dietary protein. Nutrients. 2021. https://doi.org/10.3390/nu13093193.

71. Clasey JL, Easley EA, Murphy MO, et al. Body mass index percentiles versus body composition assessments: challenges for disease risk classifications in children. Front Pediatr. 2023;11:1112920. https://doi.org/10.3389/fped.2023.1112920.

72. Endocrine Society. BMI alone may not be a sufficient indicator of metabolic health. https://www.endocrine.org/news-and-advocacy/news-room/2023/endo-2023-press-visaria. Accessed 21 Jun 2023.

73. Andes LJ, Cheng YJ, Rolka DB, Gregg EW, Imperatore G. Prevalence of prediabetes among adolescents and young adults in the United States, 2005–2016. JAMA Pediatr. 2020;174: e194498. https://doi.org/10.1001/jamapediatrics.2019.4498.

74. Sanyaolu A, Okorie C, Qi X, Locke J, Rehman S. Childhood and adolescent obesity in the United States: a public health concern. Glob Pediatr Health. 2019. https://doi.org/10.1177/2333794x19891305.

75. Badesha HS, Bagri G, Nagra A, Nijran K, Singh G, Aiyegbusi OL. Tackling childhood overweight and obesity after the COVID-19 pandemic. Lancet Child Adolesc Health. 2021;5:687–8. https://doi.org/10.1016/s2352-4642(21)00204-2.

76. Jha S, Mehendale AM. Increased incidence of obesity in children and adolescents post-COVID-19 pandemic: a review article. Cureus. 2022;14: e29348. https://doi.org/10.7759/cureus.29348.

77. Endocrine Society. Type 2 diabetes increased among youth during and after COVID-19 pandemic. https://www.endocrine.org/news-and-advocacy/news-room/2023/endo-2023-press-bell-sambataro. Accessed 21 Jun 2023.

78. Boers E, Afzali MH, Newton N, Conrod P. Association of screen time and depression in adolescence. JAMA Pediatr. 2019;173:853–9. https://doi.org/10.1001/jamapediatrics.2019.1759.

79. Mannan M, Mamun A, Doi S, Clavarino A. Prospective associations between depression and obesity for adolescent males and females—a systematic review and meta-analysis of longitudinal studies. PLoS ONE. 2016;11: e0157240. https://doi.org/10.1371/journal.pone.0157240.

80. Ali MK, Echouffo-Tcheugui J, Williamson DF. How effective were lifestyle interventions in real-world settings that were modeled on the Diabetes Prevention Program? Health Aff (Millwood). 2012;31:67–75. https://doi.org/10.1377/hlthaff.2011.1009.

81. Ferreira Silva RM, Mendonça CR, Azevedo VD, Raoof Memon A, Noll P, Noll M. Barriers to high school and university students' physical activity: a systematic review. PLoS ONE. 2022;17: e0265913. https://doi.org/10.1371/journal.pone.0265913.

82. Nally S, Ridgers ND, Gallagher AM, Murphy MH, Salmon J, Carlin A. "When you move you have fun": perceived barriers, and facilitators of physical activity from a child's perspective. Front Sports Act Living. 2022;4: 789259. https://doi.org/10.3389/fspor.2022.789259.

83. Yungblut HE, Schinke RJ, McGannon KR. Views of adolescent female youth on physical activity during early adolescence. J Sports Sci Med. 2012;11:39–50.

84. Abi Nader P, Hilberg E, Schuna JM, John DH, Gunter KB. Teacher-level factors, classroom physical activity opportunities, and children's physical activity levels. J Phys Act Health. 2018;15:637–43. https://doi.org/10.1123/jpah.2017-0218.

85. Pulling Kuhn A, Kim E, Lane HG, et al. Associations between elementary and middle school teachers' physical activity promoting practices and teacher- and school-level factors. Int J Behav Nutr Phys Act. 2021;18:66. https://doi.org/10.1186/s12966-021-01129-4.

86. Weaver RG, Webster CA, Beets MW, et al. Initial outcomes of a participatory-based, competency-building approach to increasing physical education teachers' physical activity promotion and students' physical activity: a pilot study. Health Educ Behav. 2018;45:359–70. https://doi.org/10.1177/1090198117731600.

87. Gao J, Zheng P, Jia Y, et al. Mental health problems and social media exposure during COVID-19 outbreak. PLoS ONE. 2020;15: e0231924. https://doi.org/10.1371/journal.pone.0231924.

88. Wang Y, Lynne SD, Witherspoon D, Black MM. Longitudinal bidirectional relations between body dissatisfaction and depressive symptoms among Black adolescents: a cross-lagged panel analysis. PLoS ONE. 2020;15:e0228585. https://doi.org/10.1371/journal.pone.0228585.

89. Huard Pelletier V, Lessard A, Piché F, Tétreau C, Descarreaux M. Video games and their associations with physical health: a scoping review. BMJ Open Sport Exerc Med. 2020;6: e000832. https://doi.org/10.1136/bmjsem-2020-000832.

90. Meng SQ, Cheng JL, Li YY, et al. Global prevalence of digital addiction in general population: a systematic review and meta-analysis. Clin Psychol Rev. 2022;92: 102128. https://doi.org/10.1016/j.cpr.2022.102128.

91. Hamidullah S, Thorpe HHA, Frie JA, McCurdy RD, Khokhar JY. Adolescent substance use and the

brain: behavioral, cognitive and neuroimaging correlates. Front Hum Neurosci. 2020;14:298. https://doi.org/10.3389/fnhum.2020.00298.

92. Cepni AB, Ledoux TA, Johnston CA. Screen media: a powerful reinforcement. Am J Lifestyle Med. 2020;14:126–9. https://doi.org/10.1177/1559827619892543.

93. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002;1:13–20. https://doi.org/10.1151/spp021113.

94. Yarnall KS, Pollak KI, Østbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? Am J Public Health. 2003;93:635–41. https://doi.org/10.2105/ajph.93.4.635.

95. Schauer PR, Bhatt DL, Kirwan JP, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med. 2017;376:641–51. https://doi.org/10.1056/NEJMoa1600869.

96. Eli Lilly and Company. A study of tirzepatide (LY3298176) on the reduction on morbidity and mortality in adults with obesity (SURMOUNT-MMO). ClinicalTrials.gov Identifier: NCT05556512. https://classic.clinicaltrials.gov/ct2/show/NCT05556512. Accessed 12 Jul 2023.

97. Khan SS, Brewer LC, Canobbio MM, et al. Optimizing prepregnancy cardiovascular health to improve outcomes in pregnant and postpartum individuals and offspring: a scientific statement from the American Heart Association. Circulation. 2023;147:e76–91. https://doi.org/10.1161/cir.0000000000001124.

98. Lancet T. Diabetes: a defining disease of the 21st century. Lancet. 2023;401:2087. https://doi.org/10.1016/s0140-6736(23)01296-5.