



Evaluating Natural Experiments that Impact the Diabetes Epidemic: an Introduction to the NEXT-D3 Network

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Accepted: 11 April 2022 / Published online: 22 July 2022

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Abstract

Purpose of Review Diabetes is an ongoing public health issue in the USA, and, despite progress, recent reports suggest acute and chronic diabetes complications are increasing.

Recent Findings The Natural Experiments for Translation in Diabetes 3.0 (NEXT-D3) Network is a 5-year research collaboration involving six academic centers (Harvard University, Northwestern University, Oregon Health & Science University, Tulane University, University of California Los Angeles, and University of California San Francisco) and two funding agencies (Centers for Disease Control and Prevention and National Institutes of Health) to address the gaps leading to persisting diabetes burdens. The network builds on previously funded networks, expanding to include type 2 diabetes (T2D) prevention and an emphasis on health equity. NEXT-D3 researchers use rigorous natural experiment study designs to evaluate impacts of naturally occurring programs and policies, with a focus on diabetes-related outcomes.

Summary NEXT-D3 projects address whether and to what extent federal or state legislative policies and health plan innovations affect T2D risk and diabetes treatment and outcomes in the USA; real-world effects of increased access to health insurance under the Affordable Care Act; and the effectiveness of interventions that reduce barriers to medication access (e.g., decreased or eliminated cost sharing for cardiometabolic medications and new medications such as SGLT-2 inhibitors for Medicaid patients). Overarching goals include (1) expanding generalizable knowledge about policies and programs to manage or prevent T2D and educate decision-makers and organizations and (2) generating evidence to guide the development of health equity goals to reduce disparities in T2D-related risk factors, treatment, and complications.

Keywords Natural experiments · Diabetes · Policy · Health equity · Health disparities · Social determinants of health

This article is part of the Topical Collection on *Diabetes Epidemiology*

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Introduction

More than 34 million people in the USA have diabetes, the majority (90–95%) of whom have type 2 diabetes (T2D) [1••]. An additional 88 million US adults have prediabetes, a serious health condition that increases the risk of developing T2D, heart disease, and stroke [2]. Of concern, more than 8 in 10 of these individuals are not aware that they have prediabetes [3]. Diabetes management and complications improved between 1990 and 2010 [4, 5], likely due to advances in acute clinical care, improvements in health care system performance and care integration, and health promotion efforts directed at people with diabetes as well as risk factor management directed at patients with T2D [5]. However, the percentage of patients who achieved simultaneous glycemic, blood pressure, and lipid control (considered the key factors for well-controlled diabetes) plateaued in 2010. In subsequent years, the percentages of hemoglobin A1c values < 7% or blood pressure values less than 140/90 mmHg among patients with diabetes have declined [6]. This regression in the effectiveness of diabetes management has been accompanied by a resurgence of diabetes complications over the past decade, particularly among young and middle-aged adults [7]. For example, the number of diabetes-related lower-extremity amputations in the USA increased between 2010 and 2015 (reversing by more than one-third the prior 20-year decline) [8]. In addition, hyperglycemia-related emergency department visits doubled, hospitalizations increased by 73%, deaths increased by 55%, and long-term improvements in end-stage kidney disease, acute myocardial infarction, and stroke stalled after 2010 [9].

Although this resurgence in diabetes complications can be seen nationally, wide inequities in diabetes prevalence and diabetes-related complication rates exist across the US population. For example, individuals of lower socioeconomic status (measured via education and income levels) have more limited access to care and preventive services [10]. Compared to individuals with higher socioeconomic status, this population is also more likely to have undiagnosed diabetes or prediabetes [2], higher-risk health behaviors, suboptimal glycemic management, worse cardiometabolic outcomes [7, 11–14], and shorter life expectancy. Disparities are also seen across racial and ethnic groups, with higher rates of diabetes seen among non-Hispanic black, Hispanic, and American Indian/Alaska Natives as compared to non-Hispanic whites and Asian populations [15]. Policy changes impacting broader aspects of organizations and financing of health services may also influence risk of T2D and diabetes complications. For example, although the number of uninsured individuals has declined with the introduction of the Affordable Care Act (ACA),

the proliferation of high-deductible health plans (HDHPs) in recent years may contribute to reductions in acute care access and retinopathy screening, particularly among low-income individuals [16, 17]. Income-related disparities in access to and utilization of resources that support healthy lifestyle behaviors shown to lower diabetes risk also exist. Healthy eating is one such example; for instance, the number of US adults who meet recommended fruit and vegetable intake levels is low (1 in 10 adults) and varies across socioeconomic subgroups, with lower consumption seen among adults experiencing poverty [18].

It may be valuable to find ways to enhance access to preventive services and care for populations at higher risk of T2D and its complications, especially those facing adverse social conditions that worsen health outcomes. Improving outcomes for the diverse and changing diabetes population requires a continued focus on clinical care (risk factor management), health system improvements (care coordination), health promotion and prevention efforts (lifestyle modification support), and societal factors (population-wide policies that improve diabetes risk factors and underlying social determinants of health [SDOH]) [5]. Many such programs and policies have been implemented in health care and non-health care settings and are considered “natural experiments”. Evaluations of these broad population-based natural experiments can demonstrate the impact of real-world interventions on diabetes-related health outcomes and costs as well as identify key population subgroups most likely to benefit.

History, Description, and Goals of the NEXT-D3 Network

The Natural Experiments for Translation in Diabetes 3.0 (NEXT-D3) Network is a 5-year research collaboration among researchers at six academic centers (Harvard University, Northwestern University, Oregon Health & Science University, Tulane University, University of California Los Angeles, and University of California San Francisco) that uses natural experiment study designs to evaluate changes in policy and practice, with a focus on diabetes-related outcomes. The network aims to provide a platform and framework for natural experiment research focused on diabetes and builds upon activities of the NEXT-D (2010–2015) [19•] and NEXT-D2 (2015–2020) [20•] networks that were funded by the Centers for Disease Control and Prevention (CDC)’s Division of Diabetes Translation, the National Institute of Digestive and Diabetes and Kidney Diseases (NIDDK), and the Patient-Centered Outcomes Research Institute (PCORI). Reports from NEXT-D and NEXT-D2 have described the impact of population-level policies (e.g., integrating diabetes screening prompts into city-wide

electronic medical records, employer-sponsored lifestyle modification programs, targeted cost-sharing reductions for diabetes care, HDHPs, insurance expansion, universal preventive coverage for obesity screening, Medicaid innovations in care for high-cost, and high-need patients) on diabetes care, outcomes, and costs [16, 21–36].

NEXT-D3 is funded by CDC and NIDDK through 2025. A major goal of NEXT-D3 is to generate knowledge about policies and programs to manage or prevent diabetes to provide generalizable information and educate decision-makers and organizations. Using real-world data, NEXT-D3 will provide estimates regarding reach, uptake, effectiveness, and long-term impacts of policies and practice innovations from diverse, non-trial contexts. A secondary goal is to generate evidence to guide health equity priorities to reduce disparities in diabetes-related risk factors and diabetes management complications. To facilitate this, all NEXT-D3 sites will determine how measures of SDOH affect the natural experiments they study. CDC and NIDDK collaborate with the investigators on various aspects of study methods, metrics, and dissemination efforts to maximize the robustness of research findings, promote rapid dissemination, and increase the potential for implementation of successful policies/programs. Additional details regarding NEXT-D3, including information for patients, researchers, and policymakers, are available on the NEXT-D3 website (<https://nextd3.healthsciences.ucla.edu/>).

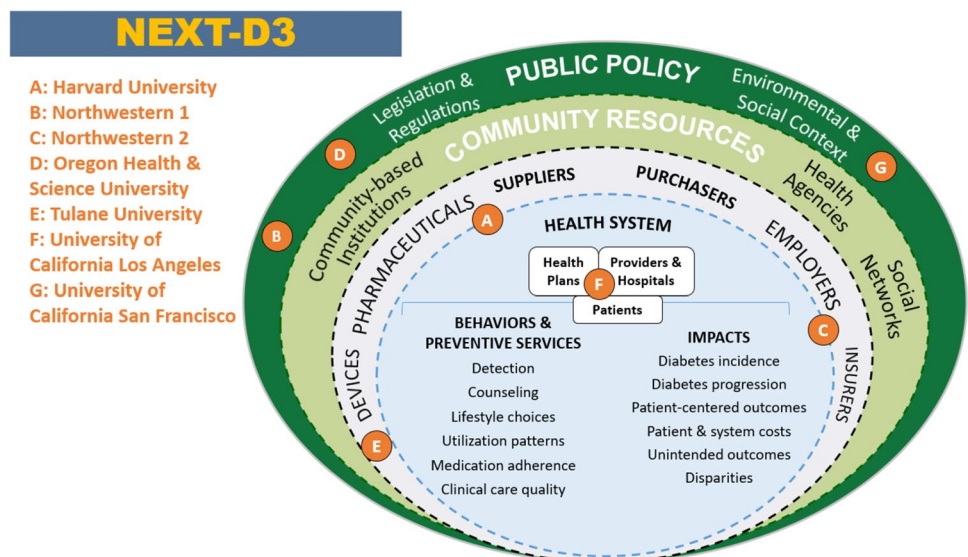
NEXT-D3 Conceptual Framework

The original NEXT-D Network developed a conceptual framework to help researchers and policy makers carefully consider the wide spectrum of programs and policies that

might impact T2D prevention as well as diabetes management and outcomes [20, 36]. We placed each of the NEXT-D3 studies into this framework (Fig. 1). The figure shows the primary approach of each of the studies and does not capture any additional effects the studies may have within the conceptual framework. Of the six participating research centers, one of them (Northwestern University) is studying two distinct natural experiments and therefore is represented by two letters within two different circles on the figure (B and C). Programs can be implemented by and within individual health systems, represented by the innermost blue circle. Other programs are initiated by suppliers and purchasers of health care, such as private employers and private or public health insurers, represented by the next surrounding white circle. Depicted in the third light green circle are institutions in the broader community, including religious, social service, civic, and commercial organizations that provide resources for and support programs designed to prevent T2D or to improve diabetes care; none of the NEXT-D3 studies are currently in this realm. Finally, the laws and regulations that shape the economic, physical, social, and cultural environments of Americans with or at risk for diabetes are represented in the outermost dark green circle.

As mentioned above, a key feature of NEXT-D3 is an explicit focus on SDOH and health equity. The World Health Organization defines SDOH as the “complex, integrated, and overlapping social structures and economic systems (e.g., the social environment, physical environment, health services, and structural and societal factors) that are responsible for most health inequities (disparities) around the world” [37]. In NEXT-D2, the research teams began to advance the knowledge base of how rigorously evaluated population-based programs or policy changes can influence disparities in T2D prevalence and diabetes outcomes [38],

Fig. 1 Conceptual framework for NEXT-D3



- A: Harvard University
- B: Northwestern 1
- C: Northwestern 2
- D: Oregon Health & Science University
- E: Tulane University
- F: University of California Los Angeles
- G: University of California San Francisco

and NEXT-D3 aims to continue this in a more explicit and focused way, with some projects directly intervening on SDOH. A NEXT-D3 subcommittee, comprised of representatives from each study site, is also working to develop a set of standardized and validated SDOH measures that can be used across the network.

Below, we describe the individual research projects being conducted by NEXT-D3 researchers, each of which focuses on T2D prevention or treatment of diabetes and/or its complications (Table 1). Each project evaluates a policy or program using specific, well-defined research questions and employs natural experiment research design to reduce bias from confounding, such as controlled pre/post or interrupted time series. The projects fall under three major themes: health insurance expansion, health care financing and payment models, and health care and policy innovations to address SDOH.

Health Insurance Expansion

Effects of Insurance Expansion Under the ACA on Medium and Long-Term Diabetes Diagnosis, Severity, Health Outcomes, and Costs (Northwestern University, Part 1)

The first part of the Northwestern University projects will examine the effects of insurance expansion on diabetes-related outcomes. The ACA substantially reduced the number of uninsured persons, especially in Medicaid expansion states and among poorer segments of the population, who were more likely to be uninsured prior to the ACA [39]. Understanding the health and economic effects of Medicaid expansion can inform policies for diabetes care, for other chronic conditions where outcomes can be affected by improved access to care and medical management, and for potential reduction of disparities in health outcomes. The Northwestern study will examine the medium- and long-term effects of gaining insurance under the ACA, both through Medicaid expansion and under the individual insurance exchanges, on diabetes diagnosis, treatment, severity, health outcomes, and costs.

Assess Insurance Coverage Expansion on Diabetes Complications (ACE-D, Oregon Health & Science University)

Analyses of the short-term impact of Medicaid expansion demonstrated increased access to preventive care and improved management of T2D [40–42]. However, there is limited information on the longer-term effects of Medicaid expansion or the health outcomes for patients who gain and lose Medicaid coverage due to changes in Medicaid eligibility. The Oregon Health & Science University study will analyze data from over 280,000 patients within the national ADVANCE (Accelerating Data Value Across

a National Community Health Center Network) clinical research network of community health centers, comparing outcomes for patients from states that expanded Medicaid with outcomes for patients from states that did not expand Medicaid, as well as examining patients with continuous insurance coverage, unstable insurance coverage, and no insurance coverage. Outcomes will include acute and chronic diabetes-related complications as well as mortality. The analyses will also assess whether individual-level and/or community-level SDOH moderate the relationship between Medicaid expansion and health outcomes.

Health Care Financing and Payment Models

Long-Term Impact of Reduced Patient Out-of-Pocket Costs on Diabetes Complications (Harvard University)

HDHPs that require patients to pay up to \$1000–7000 out of pocket (OOP) per year are now the predominant private health insurance arrangement [43]. Increased OOP costs under HDHPs are associated with delays in seeking care [16, 27], increases in acute, preventable diabetes complications [16], and increases in high-severity emergency department visits among low-income HDHP members [17]. HDHPs with health savings accounts (HSA-HDHPs) typically make antidiabetic and other cardioprotective medications subject to the full deductible. For example, the average HSA-HDHP insulin user pays \$700–1000 per year for the medication, 2–3 times more than those without an HSA-HDHP account [44]. Because of concerns about such cost barriers, an increasing number of employers are purchasing preventive drug lists (PDLs) that lower OOP costs for cardioprotective medications or are switching from an HDHP to more generous lower-deductible health plans [26]. The Harvard site's NEXT-D2 study found that PDLs increase short-term cardioprotective medication use, especially among low-income HDHP members. PDLs that reduce medication cost may prevent rationing and underuse of antiglycemic medications among low-income HDHP members [26]. In NEXT-D3, Harvard will analyze a 16-year rolling cohort using a combination large commercial and Medicare Advantage health insurance claims database with members from all 50 states and the District of Columbia. Applying an interrupted time series with comparison series difference-in-difference design, the team will determine whether adopting employer PDLs or switching from HDHPs to low-deductible plans is associated with long-term reductions in acute and chronic diabetes complications, including among low-income and high-morbidity members. Finally, the team will assess the effect of state policies that reduce insulin OOP costs on insulin use and diabetes complications.

Table 1 Selected characteristics of NEXT-D3 projects

Team/project	Intervention	Data source(s)	Setting and population	Analytic method(s)	Outcomes	Social determinants of health variables
Harvard University	Employer adoption of preventive drug lists and low-deductible health plans State adoption of legislation to reduce insulin out-of-pocket costs	A large and commercial and Medicare Advantage administrative claims database	10 million members per year of data	Interrupted time series with control series	<ul style="list-style-type: none"> Utilization of care Quality measures (visits, medication use, screenings) Acute preventable diabetes complications Micro-/macrovascular complications Advanced micro- and macrovascular disease complications 	<ul style="list-style-type: none"> Urban/rural Area-level poverty and education
Northwestern University (Study 1)	ACA insurance expansion	EHR and Medicaid data from Illinois, Wisconsin, and Indiana	8.7 M adult patients (<65 years) in EHR, including 1.3 M covered by Medicaid and 700,000 with diabetes	DiD/discontinuity with matched controls	<ul style="list-style-type: none"> HbA1c, blood pressure, lipids, BMI Micro-/macrovascular complications Mortality 	<ul style="list-style-type: none"> Community-level deprivation and poverty measures
Northwestern University (Study 2)	State policies that lower barriers for initiation and use of SGLT2i	Administrative data files for UHG Medicaid managed care organizations (MCOs)	~500,000 adult Medicaid beneficiaries in United-Health Group managed care plans nationally	Pre/post DiD with matched comparators	<ul style="list-style-type: none"> SGLT2i drug class fill rate Mean SGLT2i cost per enrollee Acute preventable diabetes complications Hospitalization for CHF Hospitalization for all causes Rate of genital infection Nontraumatic lower-extremity amputations Mean total healthcare expenditures 	<ul style="list-style-type: none"> Census SES measures
Oregon Health & Science University	ACA Medicaid expansion, stratified by stability of insurance and SDOH	EHR data from ADVANCE	177,125 adults with diabetes (in 22 Medicaid expansion states) 104,849 adults with diabetes (in 7 non-expansion states)	Pre/post DiD with matched comparators	<ul style="list-style-type: none"> Acute preventable diabetes complications Chronic diabetes complications All-cause mortality 	<ul style="list-style-type: none"> Patient-level race/ethnicity Area-level urban/rural, poverty, social deprivation index, built environment (density, population, parks, food access), infrastructure (plumbing, age of structures, ozone)

Table 1 (continued)

Team/project	Intervention	Data source(s)	Setting and population	Analytic method(s)	Outcomes	Social determinants of health variables
Tulane University	Zero-dollar copayment for diabetes-related medications	BCBS-LA claims and EHR data from REACHnet	Residents of Louisiana, age 18+, fully insured by BCBS-LA	Pre/post DiD with matched controls, analysis of heterogeneity of treatment effects	<ul style="list-style-type: none"> Medication adherence Glycemic control Complications Health care utilization Cost-effectiveness 	<ul style="list-style-type: none"> Patient-level race/ethnicity
University of California Los Angeles	UnitedHealthcare national care coordination program (payer-initiated program to assist with medical and behavioral issues and SDOH)	UnitedHealthcare and Optum administrative claims	115,771 adults with diabetes 388,946 adults without diabetes	Intention-to-treat analysis of RCT Per-protocol IV analysis using randomization status as the instrument	<ul style="list-style-type: none"> Utilization of care Diabetes processes of care Adherence to medications Acute diabetes complications Microvascular complications Macrovascular complications Costs of care Diabetes control (HBA1c) 	<ul style="list-style-type: none"> Patient-level race/ethnicity
University of California San Francisco	Nutrition assistance (SNAP/WIC) policy changes and expansion SNAP: new access for SSI patients WIC: change from paper to electronic access	California Department of Social Services and Office of Health Planning: discharges from all California hospitals UC data warehouse California birth cohort	California databases: 393,000 with diabetes UC data warehouse: 20,000 with diabetes and 75,000 with pre-diabetes	Observational, within group	<ul style="list-style-type: none"> DM/GDM incidence Utilization of care Birth outcomes (gestational weight gain, birth weight, etc.) Diabetes control (HBA1c) Cost-effectiveness 	<ul style="list-style-type: none"> Urban/rural Percent under federal poverty level Race/ethnicity Median household income Rate of high school graduation Unemployment rate Geographic price index Median rent

Abbreviations: ACA Affordable Care Act, EHR electronic health records, DiD difference-in-difference, HBA1c hemoglobin A1c, BMI body mass index, UHG United Health Group, MCO managed care organization, SGLT2i sodium/glucose cotransporter-2 inhibitors, CHF congestive heart failure, SES socioeconomic status, SDOH social determinants of health, BCBS-LA Blue Cross and Blue Shield of Louisiana, REACHnet Research Action for Health Network, RCT randomized controlled trial, IV analysis instrumental variable analysis, SNAP Supplemental Nutrition Assistance Program, WIC Women, Infants, and Children, SSI Supplemental Security Income, UC University of California, GDM gestational diabetes mellitus

Effects of Medicaid Coverage and State-Level Delivery Approaches on Health Care Quality, Outcomes, and Costs for Adults with Diabetes (Northwestern University, Part 2)

The second part of the Northwestern project focuses on state-level variation in Medicaid managed care policies that shape access to newer classes of diabetes medications, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, which have unique protective health benefits but are significantly more costly. State Medicaid agencies steward limited public resources while attempting to balance access, quality, outcomes, and cost in their Medicaid programs, particularly for patients with costly chronic conditions such as diabetes. Most states administer Medicaid programs in partnership with managed care organizations, and policies to balance access to costlier medications are enacted by both the Medicaid agency and managed care partners in ways that differ in virtually every state [45]. This study will integrate Medicaid managed care administrative data from multiple states to compare effects on medication starts, acute diabetes complications, and net health care costs as different state programs enact policies that are designed to lower barriers for the initiation and use of SGLT2 inhibitors (e.g., relaxing prior authorization requirements; extending refill quantity limits from 30 to 90 days). It is anticipated that this natural experiment will help states and managed care partners identify select policy approaches that may increase pharmaceutical costs for patients with diabetes by expanding access to SGLT2 inhibitors, but by doing so, result in more favorable and equitable health outcomes, as well as lower overall diabetes-related health expenditures, particularly for vulnerable patients at the highest risk for avoidable cardiovascular and renal complications.

Louisiana Experiment to Address Diabetes: Zero-Dollar Copayment (LEAD-ZDC) for Improving Disease Management (Tulane University)

Nonadherence to prescribed antidiabetic medications, anti-hypertensives, and statins is associated with poorer glycemic control, increased risk of diabetes complications, and greater health care costs [46]. While patients have various reasons for nonadherence, one of the primary reasons is because they cannot afford their medications [46]. Cost-related nonadherence has been closely linked to SDOH, including food insecurity and financial burden [47]. Blue Cross and Blue Shield of Louisiana has instituted a value-based benefit design (in which health insurance is structured in a way that incentivizes and drives patients and providers toward the most valuable services: those with the most benefit relative to cost) with zero-dollar copayments for selected prescription medications for its fully insured members [46]. This study will evaluate the effects of the zero-dollar copayment (ZDC)

program on medication adherence, glycemic control, rates of diabetes complications, and health care utilization using claims and electronic health records (EHR) data. Additionally, the study will examine barriers and facilitators influencing how the program is implemented and perceived by patients and health care providers. Lastly, these analyses will examine the short-term cost-effectiveness of the zero-dollar copayment program from both health system and societal perspectives and will use simulation approaches to model cost-effectiveness over a 40-year time period.

Health Care and Policy Innovations to Address SDOH

A Pragmatic Nationwide Randomized Controlled Trial of Coordinated Medical, Behavioral, and Social Services to Improve Care and Utilization Among High-Cost, High-Need Insured Patients with Diabetes (University of California Los Angeles)

University of California Los Angeles and UnitedHealthcare (UHC) are partnering to evaluate a national care coordination program for high-cost, high-need commercially insured UHC members. This care coordination program was launched in 2015 and aims to provide “whole-person care,” integrating intensive medical, behavioral, and social support at a community level to address barriers to access in addition to SDOH, including food and housing insecurity. UHC designed and instituted a patient-level, pragmatic randomized controlled trial (RCT) of this program and has randomized over 500,000 individuals to either the national care coordination program or usual care. Using administrative claims data, this study will analyze the effects of this program on multiple outcomes using an intention-to-treat RCT analysis as well as an instrumental variable analysis with randomization status as the instrument. These analyses will evaluate whether the program is associated with reductions in diabetes complications, acute care utilization, and costs of care.

Longitudinal Food security Experiments via Supplemental Assistance with Nutrition for Diabetes (LIFESPAN-D, University of California San Francisco)

Food insecurity is a common and potent mediator in the development of T2D and diabetes-related complications among low-income populations in the USA [48]. Food insecurity pressures low-income individuals with T2D to consume inexpensive food of poor dietary quality, presenting difficult choices between paying more for higher-quality food or paying for medicine or other expenses such as housing or heat [49–51]. Furthermore, food insecurity among pregnant women is associated with an increased risk of gestational diabetes and other pregnancy-related complications

[52]. Longitudinal Food security Experiments via Supplemental Assistance with Nutrition for Diabetes (LIFESPAN-D) is composed of two substudies. The first substudy relates to older low-income adults. In 2019, California began to allow low-income, older, and/or disabled individuals receiving Supplemental Security Income (SSI)—populations with a high prevalence of food insecurity and risk for T2D and diabetes complications—to receive simultaneous benefits from the Supplemental Nutrition Assistance Program (SNAP, formerly known as food stamps). This substudy will harmonize and analyze statewide longitudinal datasets (including hospital discharge data) using a quasi-experimental pre/post design to determine whether the addition of the SNAP benefit for older low-income adults is associated with county-level reductions in multiple outcomes, including diabetes-related hospitalizations, individual-level improvements in cardiometabolic control among individuals with T2D, and reduced incidence of T2D among individuals with prediabetes. The second substudy will evaluate the effects of a separate policy that allowed recipients of the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)—a program that provides nutrition support to low-income pregnant and postpartum women and children under the age of 5—to receive an electronic benefit card rather than paper vouchers. The substudy will examine whether this policy change leads to increased WIC benefit uptake and reductions in gestational diabetes and other pregnancy-related complications among pregnant women and in unfavorable birth outcomes associated with diabetes risk in their children such as low birth weight.

Discussion

The NEXT-D3 Network is designed to advance the field of natural experimental research in diabetes using rigorous quasi-experimental approaches. The answers to the wide variety of research questions in NEXT-D3, with projects specifically selected to evaluate programs and policies designed to improve diabetes prevention and care in the USA, will be an important addition to our knowledge about the impact of clinical care and broad social policies on diabetes outcomes and health equity nationally.

As mentioned above, an important contribution of this effort will be a coordinated approach to address measurement and modeling of SDOH in analyses of T2D prevention and diabetes treatment. NEXT-D and NEXT-D2 highlighted that the impacts of health care system changes are often more pronounced in certain segments of the population and that larger effects in smaller segments of the population tend to be blunted as averages of the larger population-wide analyses or due to health care and payer innovations being too far downstream to make a significant impact on disparities.

In NEXT-D3, research into the upstream determinants of diabetes and health disparities will help to provide a better understanding of the impact on programs and policies across diverse subpopulations. This will be accomplished by incorporating SDOH measures into the research questions, and by using a set of standardized and validated SDOH measures across all study sites.

These studies will use innovative methodologies to reduce confounding and biases (such as difference-in-difference, interrupted time series with more than two time points, and propensity score methods) and novel data systems (such as administrative claims, EHRs, and mortality data from state registries, obituaries, and the Social Security Administration) that have the potential to focus on the specific mechanisms that help patients, clinicians, systems, and policymakers make changes, particularly for low-income and vulnerable populations. For example, currently, many social assistance programs lack rigorous evidence of their effectiveness. But innovative studies such as the UC San Francisco project, which combines state-level social services data (e.g., the SNAP benefit) with longitudinal health care data, can guide the design of social assistance programs in order to improve outcomes for people with prediabetes, gestational diabetes, or T2D. In order to study the effects of the 2019 California statewide policy that allowed recipients of SSI to be eligible for SNAP, the UCSF team is shepherding an unprecedented demonstration of integration to link data across three sources including the California Department of Social Services (which administers SSI and SNAP), the California Department of Health and Human Services (which administers Medicaid) and the California Department of Health Care Access and Information (which manages hospital discharge data). The research will harness this linked SSI-SNAP-Medicaid claims dataset to examine the impact of new SNAP enrollment on all-cause and diabetes-related emergency room visits, hospitalizations, and associated costs.

As another example of the innovative methodologies and linkages being used in NEXT-D3, the Oregon Health & Sciences University project will compare the effects of the ACA Medicaid expansion on acute diabetes complications in communities with varying levels of resources and stability (e.g., access to supermarkets/large grocery stores and percentage of vacant housing units) by linking community-level data to EHR data for individual patients, the first study of its kind to link EHR records to death records from the DATAVANT mortality files to assess the impact of the ACA on mortality risk among patients with diabetes. Additionally, the Oregon Health & Sciences University team is integrating information from neighborhood geospatial data and linking these indicators to every patient's EHR information. The community-level data derived from multiple public data sources will

provide a comprehensive library of contextual indicators, and identifying neighborhood characteristics associated with different outcomes for newly insured patients with diabetes will provide important information for state and local health departments. In terms of innovative methodologies, the Harvard site is using novel combinations of rigorous quasi-experimental study designs and statistics. This includes a rigorous and validated two-level (employer and member) matching approach combining exact and entropy balancing to create closely matched study groups. Another advance is matching on the functional form of the baseline trend, a cutting-edge approach shown to approximate estimates from randomized controlled trials.

NEXT-D3 researchers will use patient perspectives as a way to put findings into context; this will be another contribution of NEXT-D3. For example, the Tulane study is a unique partnership between health plans, patients, and researchers in Louisiana to design the study of zero-dollar copayments for diabetes-related medications and interpret the results, with the goal of optimizing the design of the LEAD-ZDC benefit and communication/messaging plans in order to achieve optimal patient outcomes.

Additionally, data on health care costs and cost-effectiveness are an important part of natural experiments. Currently, there is a large body of literature on the cost-effectiveness of interventions to manage diabetes at the individual level, such as screening, pharmacological, and surgical approaches [53]. By contrast, there is a relative lack of cost-effectiveness research and knowledge on these more upstream, population-based approaches to T2D prevention [54], which may limit the extent to which policy recommendations can be made for these population-based approaches. In particular, more studies that address the cost-effectiveness of interventions in real-world settings. Most knowledge to date comes from randomized controlled trials or computer simulation models—specifically, factors such as coverage for the intervention in question (access) or whether the risk reduction in real life is similar to what was observed in trials and models—may be beneficial. Natural experiments, in which data are directly observed and reflect the “true” behavioral change of the population as a result of interventions, can strengthen the current knowledge base on the cost-effectiveness of population-based interventions.

Nonetheless, it is important to acknowledge the challenges of natural experiments, such as problems of attrition, missing data, and a lack of comparability between the exposed and unexposed groups. Additionally, as an emerging field, the linkage of health insurance claims and electronic health records databases faces both challenges (e.g., discordance of records between data sources) and opportunities to study health policy intervention that targets primary care. Linking population-based data sources such as Medicare claims data to EHR allows researchers

to leverage the complementary advantages of each data source to enhance study validity and data completeness.

The NEXT-D3 Network will disseminate study findings through multiple channels, including a website (<https://nextd3.healthsciences.ucla.edu/>) with a coordinated Twitter feed (<https://twitter.com/NetworkNextd>) with contributions from all six participating research sites. All published studies will be accompanied by a “visual abstract”—a type of infographic intended to make findings of the study more straightforward and accessible to broad audiences, including members of the lay community. The network will also provide webinars showcasing key results when they become available, inviting clinicians, policymakers, and representatives from CDC and NIDDK to participate.

An advantage of the NEXT-D3 Network structure is the compilation of detailed, longitudinal data on several million patients with T2D. In addition to facilitating research on the health outcomes being studied under NEXT-D3, these data resources also position NEXT-D3 research sites to evaluate new, unforeseen natural experiments. For example, some of the data obtained by network sites predate the onset of the COVID-19 pandemic, allowing studies of how the pandemic and different community and health system responses (e.g., government stimulus responses to economic distress caused by the pandemic, telemedicine services rapidly scaled up due to the pandemic) have influenced long-term diabetes care and outcomes. These aspects are especially relevant during the current COVID-19 pandemic, which has highlighted disproportionate effects on racial and ethnic minorities, as well as on people with diabetes [55] who already have less health care access and worse diabetes-related outcomes.

Rigorous efforts to study the effectiveness of ongoing policies and programs such as those assessed under the NEXT-D3 Network can provide a mechanism to guide how we respond to the changing tide of the diabetes epidemic over the next few decades. The wide variety of research questions and data sources in NEXT-D3, with projects specifically selected to evaluate crucial diabetes-related programs and policies, can guide improvements to both clinical care and broad policies that affect people with diabetes.

Acknowledgements We are grateful for insightful and critical edits from Jean M. Lawrence, ScD, MPH, MSSA, National Institute of Diabetes and Digestive and Kidney Diseases.

Declarations

Conflicts of Interests The authors do not have existing conflict of interests.

Disclaimer The findings and conclusions are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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