

Rationale and Design of a Comparative Effectiveness Trial to Prevent Type 2 Diabetes in Mothers and Children: The ENCOURAGE Healthy Families Study

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Abstract

The number of youth with type 2 diabetes (T2D) is expected to quadruple over 4 decades. Gestational diabetes mellitus (GDM) is also increasing and is linked with development of T2D in women, and greater risk for T2D in adolescents exposed to GDM. Despite the increasing prevalence of T2D, approaches to prevent diabetes in high-risk youth and families are rare. To address this, we are conducting the Encourage Health Families Study (ENCOURAGE). This is a randomized trial evaluating the comparative effectiveness and costs of an adaptation of the Diabetes Prevention Program (DPP) directed at mothers who had GDM or prediabetes and their children. The intervention is a group-based lifestyle program which we developed and implemented in partnership with the YMCA. We are comparing the ENCOURAGE intervention targeted to 1) mothers who have had GDM or prediabetes, and 2) mothers who have had GDM or prediabetes *along with their school-aged children*. This manuscript provides 1) the rationale for a targeted approach to preventing T2D and the interventions, 2) description of the translation of the DPP curriculum, and 3) the study design and methodology. The primary aims are to determine if participation leads to 1) weight loss in high-risk mothers, and 2) youth having healthier weights and lifestyle habits. We will also evaluate costs associated with each approach. These data are essential to build a translation model of T2D prevention that is both realistic and feasible to address this growing problem in both youth and adults.

Keywords: gestational diabetes; prediabetes; obesity; dysglycemia; prevention; youth

Abbreviations:

DPP, Diabetes Prevention Program

GDM, gestational diabetes mellitus

T2D, type 2 diabetes

Introduction

A disturbing aspect of the obesity epidemic is the growing onset of type 2 diabetes (T2D) in adolescents. Between 2001 and 2009, the prevalence of T2D increased more than 30% in youth in the US.¹ At this rate, between 2010 and 2050, the number of youth with T2D will increase four-fold.² This is concerning since T2D is associated with particularly poor health outcomes in this population and increased cost of pediatric health care.

We have made tremendous progress toward understanding the risk factors for, and pathophysiology of, T2D in youth. Arguably, the most important risk factors for developing T2D as an adolescent are obesity and a family history of T2D.³ Furthermore, the presence of maternal gestational diabetes mellitus (GDM) is a potent risk factor for future T2D in both a mother and her child.⁴⁻⁸ The Treatment of Diabetes in Adolescents and Youth (TODAY) study illuminated the disease's propensity for increased tempo of progression in some youth, the difficulty in maintaining metabolic control with available treatments, and the high rates of comorbid conditions and complications.^{3, 9-13} This study also showed that T2D occurs more often in those with conferred genetic and epigenetic risk, particularly in families with lower levels of education and socioeconomic means. These findings highlight the need to prevent the condition from the outset.^{14, 15} Clinical trials in adults have demonstrated that diet and lifestyle modification are highly effective in preventing T2D, with sustained results.¹⁶⁻²¹ However, targeted approaches to reducing T2D risk in high-risk youth and families are rare.

To address the need for targeted diabetes prevention approaches with impact on high-risk youth and their families, we are conducting a study entitled "Encourage Healthy Families" (ENCOURAGE). For these reasons outlined above, we elected to target the children of women with a history of GDM or prediabetes since they represent a growing population that has a genetically defined increased risk for developing T2D sometime in their life course, especially if they develop additional risk factors such as obesity.⁴⁻⁸ We hypothesized that delivering a diabetes prevention curriculum emphasizing lifestyle modification to reduce weight and increase

physical activity to high-risk mothers and making these mothers aware of their childrens' increased risk for developing T2D would have the effect of benefiting their children, even when the children were not directly involved in program sessions. We further hypothesized that creating a program for youth to introduce healthy lifestyle choices while their mothers were in the lifestyle program would enhance the impact on family health. The ultimate goals of this project are: 1) to translate interventions targeting mothers with children who are at increased risk to determine if we can evoke "primordial prevention" i.e., mothers changing family lifestyle behaviors to reduce risk in their children (Phase 1), and 2) to test its relative cost-effectiveness against the newly-developed more child-intensive program (Phase 2). Phase 2 is designed to test two different lifestyle modification approaches that reflect different levels of both intensity and necessary resources, to achieving risk reduction of T2D in a high-risk population of women who had GDM and/or prediabetes and their children who are also at increased risk of T2D should they develop obesity.

This manuscript provides 1) the rationale for a targeted approach to preventing T2D and the interventions, 2) description of the translation of the DPP curriculum, and 3) the study design and methodology.

Research Design and Methods

Rationale for a Targeted Population Approach to Preventing T2D in ENCOURAGE: Focus on Mothers with GDM and/or Prediabetes and Their Children

The prevalence of GDM is increasing among young pregnant women as obesity continues to increase.^{22, 23} This is especially troublesome, because up to 10% of pregnancies are affected by GDM, and women with GDM have a 35-65% chance of developing T2D in the next 10-20 years.²⁴ There is growing evidence from both animal and human studies that maternal obesity and GDM is contributing to the increase in childhood obesity and T2D as a result.^{5, 25} In the largest cohort of adolescents with T2D studied in the U.S. (TODAY, n=704)

one third of the cohort was born after a pregnancy complicated by diabetes.³ In the SEARCH for Diabetes in Youth study, exposure to maternal diabetes and exposure to maternal obesity were independently associated with T2D in adolescents and overall, 47.2% of T2D in the cohort (n=79) could be attributed to intrauterine exposure to maternal diabetes and obesity.⁷ Thus, becoming obese during childhood in combination with exposure to GDM is a strong predictor of development of T2D. These facts also enable us to convey to mothers with GDM that their children have increased risk for developing T2D, an essential component of primordial prevention.

Likewise, a family history of T2D or prediabetes in a first-degree relative also puts one at increased risk for developing T2D. The presence of dysglycemia in a first-degree relative is associated with dysglycemia in offspring, even in the absence of obesity.²⁶⁻²⁸ We now know that common genetic variations associated with risk for developing β -cell dysfunction and impacting insulin sensitivity exist and confer hereditary risk for prediabetes and T2D.²⁹ The genetic factors in combination with increasing levels of obesity-related insulin resistance play an important role in the development of T2D.²⁶

For the reasons outlined here, we chose to target a high-risk population of women who had GDM and/or prediabetes and their children for the ENCOURAGE project. Studies to address the health and behavior of women with GDM and/or prediabetes are critical, not only for the health of the mother and preventing T2D, but also for investigation of the potential impact that this might have on the child who is also at increased risk for T2D. Moreover, whether or not intervention for women with GDM and/or prediabetes is efficacious in reducing risk factors for T2D in their children deserves further study and direct comparison with other programs currently designed to promote weight reduction in youth.

Rationale for the T2D Prevention Interventions in ENCOURAGE

Rigorous trials have demonstrated a clear and meaningful ability to prevent the progression of prediabetes to T2D in adults via lifestyle modification promoting modest weight loss and increased physical activity.^{30, 31} A lack of rigorously tested diabetes prevention lifestyle strategies exist that are targeted specifically toward high-risk youth. The reasons for this include the relative low prevalence of T2D as compared with adults, and the prohibitive costs of conducting such trials. Thus, reducing childhood obesity via lifestyle modification and public health efforts is widely accepted as the primary pathway to decreasing the growing prevalence of T2D in youth.

Family-based behavioral treatment is the most well-established medical intervention for the treatment of childhood obesity. Golan and colleagues published results indicating that utilizing parents as the exclusive agents of change was superior to the conventional child-focused approach.³² They went on to show durability and cost-effectiveness of this treatment modality.³³⁻³⁷ Epstein and colleagues have extensively studied family-based treatment, as well as family-based group treatment, and have shown cost benefit to treating multiple family members rather than individual-focused treatment.³⁸⁻⁴¹ Moreover, relevant precedents exist for the measureable benefits that children derive from active family involvement and pro-active parenting practices to mold behaviors in childhood by promoting reductions in the consumption of unhealthy foods and sedentary behaviors in themselves and in family members.³²⁻³⁵ Thus, we speculated that mothers with increased risk for T2D could be the “focus” of an intervention to decrease T2D risk in their children. The rationale for this is that mothers who are counseled about health risks for both themselves and their children and are given strategies to reduce these risks would be more likely motivated to make significant lifestyle and home environment changes impacting not only their risk profiles, but their children’s risk profiles as well. This is based on the observations that mothers often are more motivated to make changes to reduce risks for their children and, when coupled with awareness of their own personal risk, would result in a “trickle down” effect that ultimately impacts the entire family.

School-based and clinic-based interventions in pediatric populations have been performed with mixed results on weight loss, and few substantial outcomes on diabetes prevention have been evidenced.⁴²⁻⁴⁵ An important limitation of these studies is their lack of ability to target youth at highest risk (conferred genetic and epigenetic risk) for developing T2D, and failure to include their families. Recently, one group has demonstrated that a clinical obesity program utilizing an intensive lifestyle modification plan could promote reduction in glycemic risk markers for T2D as compared with standard clinical care in high-risk obese youth.⁴⁶ This program has demonstrated that 1) it is possible to target high-risk youth in a clinical setting, and 2) lifestyle modification can effectively reduce glycemic risk markers for T2D. Nevertheless, widespread implementation of similar programs given the cost and personnel requirements would be challenging.

We have reviewed the knowledge gained from these previous investigations and our own research, and asked what the gaps were and where interventions should be targeted. Rather than target an entire school population or all obese children, we are focused on high-risk mothers and their children. By targeting mothers and their children, we might get better cost-effectiveness. The interventions we chose to test include:

- 1) A lifestyle intervention targeting women who had GDM and/or prediabetes who have school-aged children who may also be at risk for T2D
- 2) A lifestyle intervention targeting women who had GDM and/or prediabetes which also actively includes their school-aged children in the intervention

Study Phase 1: *Translation of a Diabetes Prevention Curriculum for ENCOURAGE*

We elected to adapt the lifestyle curriculum used in the U.S. Diabetes Prevention Program (DPP) for this project.⁴⁷ This curriculum is a 16-session weekly program divided into three segments. The first focuses on strategies for monitoring food intake and reducing calories. The second teaches strategies for identifying and controlling both personal and social

cues to engage in unhealthy eating behavior. The third addresses both the role that stress plays in unhealthy eating and how to recover from lapses from the program. We chose the original DPP curriculum because it was designed to be culturally appropriate for a wide-variety of populations, and has been shown to be effective in virtually all populations studied regardless of race, gender, age, and socioeconomic status.^{31, 48-50} In addition, the DPP has been shown to be efficacious in preventing progression of diabetes in women with former GDM and prediabetes which is the target population in this project.^{17, 51, 52} We elected to use a group-based version of the DPP format that was developed by our Center to minimize the costs of intervention delivery.³¹

Building upon the evidence-based curriculum used in the DPP, we translated this curriculum so that it made reference to consideration of the weight control techniques used being applied to their families. Our group has previous experience translating the DPP curriculum to a group setting while still aiming to meet the needs of a targeted population considering the pertinent lifestyles and specific patient population-centered goals of therapy.^{31, 53} Moreover, this adapted curriculum could be implemented more broadly through the YMCA, as the DPP was implemented.^{21, 31, 54} This approach would reduce costs of implementing the program. Specifically, we took each of the 16 sessions of the Lifestyle Balance curriculum used in the DPP and modified the scripts used to reflect consideration of applying session content to family members (mothers and children) versus the individual. In the original DPP, all sessions asked the participant to consider how various themes apply to themselves. For example, in session 3, participants are asked to be a “Fat Detective” in which they try to identify the sources of fat in their personal diet. In the revised curriculum, we asked participating mothers to consider sources of fat *in their family diet*, in particular the diet fed to their child as well as for themselves. It was our intention to preserve as much of the original DPP curriculum content and focus as possible, since the evidence showed the effectiveness of this across a wide population sample. Thus, in each lesson we shifted focus from the individual to the individual

and their family with emphasis on their child at risk. All support materials and curricula worksheets were altered to reflect this change in focus to capture parental concern about the risk of their children as well as their own personal risk. We created two versions of the curriculum used in this program: one for mothers without direct involvement of their children, and another that was linked to a supplemental program for youth conducted at the same time as the program for mothers. This second curriculum had two fundamental differences from the mother-only version. First, it made mothers aware of what their children were learning in their parallel supplemental sessions. Second, it asked mothers to do at-home activities (conceptualized as homework) with their children to reinforce lesson concepts.

The children's curriculum which is unique to this project, was designed as a 16-session weekly program that introduced several themes found in the DPP curriculum adjusted for age-appropriate presentation. These included: understanding how behavior can influence health, what are sources of fat and other unhealthy nutrients in foods and how to identify them, reading food labels to understand nutritional content, making healthy food choices away from home, identifying cues that lead to unhealthy eating behaviors. In addition, each session contained both a healthy snack and a physical activity component that was adapted from the SPARKS program, an evidence-based physical education program for youth.⁵⁵ Finally, the curriculum encouraged the children to engage their parents in the form of "homework". As noted above, the parental version also contained this request. A list of session titles and brief description of the focus of each session is included in Appendix 1.

We purposefully elected to not teach parenting strategies to both preserve the integrity of the highly effective DPP format and to reduce the complexity of the intervention. While we encouraged parents and children to interact about session content and suggested behaviors via "homework", the primary focus of the intervention was to act upon the mothers to engender a sense of primordial prevention, i.e. making behavioral changes to reduce the risk in their children.

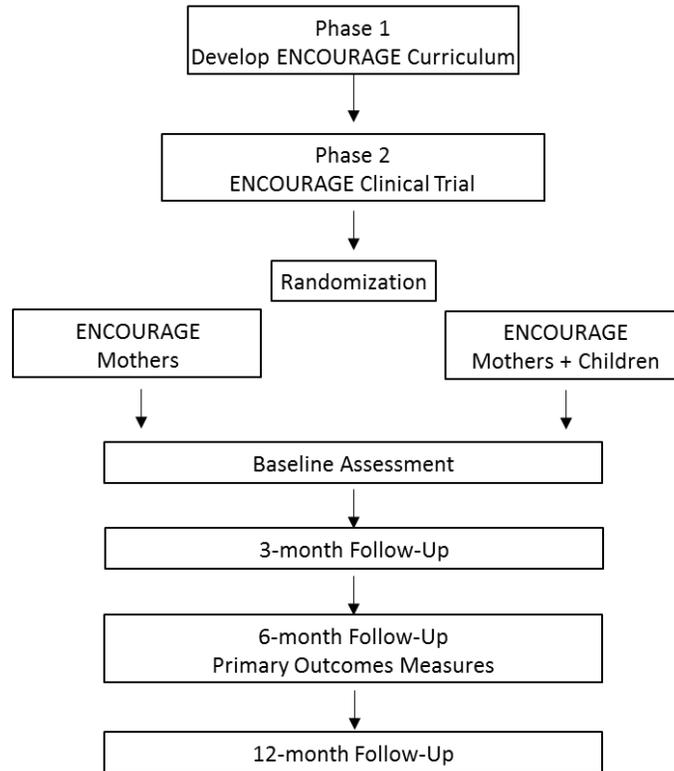
We recognize that program adherence is challenging, particularly when trying to get families as a unit involved. We have addressed this issue by offering incentives for participation. Moreover, having mothers and children attend simultaneous sessions at the YMCA reduces the potential for children to independently decide not to participate. Also, because the YMCA offers childcare services, it has been our experience that mothers are much more likely to attend even when they have other children in the family. It is directed toward children between the ages of 8-15 years. We elected to include this age range because the average age of onset of T2D in youth is approximately 14 years,³ and this was designed to be a prevention curriculum. In addition the SPARKS physical education program is responsive to this age range.⁵⁵ Included in the curriculum are weekly exercise activities intended to improve the child's overall fitness level and introduce fun ways to be physically active. We hypothesized that by also including the children in T2D prevention efforts in this arm of ENCOURAGE, we could achieve better results at T2D risk reduction than the mother-only condition. While clearly potentially more intensive than the parent only intervention, this approach also increases the complexity and associated costs.

Study Phase 2: ENCOURAGE *Program Evaluation*

Study Design

We are currently performing a controlled trial of the intervention models utilizing multiple YMCA sites in the Indianapolis area. This clinical trial has been approved by the Indiana University School of Medicine Institutional Review Board and all participants have given informed consent or assent (ClinicalTrials.gov identifier NCT01823367). The study design is illustrated in Figure 1.

Figure 1.



At least one child (aged 8-15 years) from each mother with a history of GDM and/or prediabetes is recruited to provide outcomes measures, regardless of the study arm.

Sample Size

In order to determine the necessary sample size for this study, we performed a calculation for a superiority trial using a continuous outcome (mother's weight). We aimed to detect a mean difference of 5% in the mean change of body weight at 6-month from baseline between the two intervention groups. We assumed standard deviation of 8% in the change in body weight. Using an alpha of 5%, a sample size of 42 per treatment group will have 80% power to detect the proposed mean difference. However, we will recruit 50 per group to accommodate up to 15% dropout rate, which is similar to the dropout rate we have observed in a similar study offering a similar intervention at the YMCA.³¹

Randomization

We used a stratified randomization plan based on two strata: 1) Latino versus Non-Latino, and 2) mothers with a single eligible child versus mothers with multiple eligible children. There was no priori subgroup hypotheses for this stratified randomization plan. We wanted to ensure equal distribution of ethnicity (Latino versus Non-Latino) and mothers with single versus multiple children between the two intervention arms. This provides an advantage for isolating the intervention effect from either the ethnicity and/or from multiple children participating. A stratum specific computer generated randomization list was prepared by a statistician to randomly assign study subjects in one of the two treatment groups. A block size of two was used to ensure balance in number of subjects recruited in two groups after recruiting every two subjects.

Recruitment

To identify women with recent histories of GDM and/or prediabetes, we queried the local electronic medical record (EMR) databases after obtaining Institutional Review Board approval. Women with a history of GDM and/or prediabetes and who had children 8-15 years of age were contacted soliciting their participation in ENCOURAGE. We did not require that high risk children be the direct product of a high-risk pregnancy. With attention to the generalizability of the study, the population recruited is overrepresented by women of minority status and from lower income groups. Recruitment strategies also include health fairs, community events, social media campaigns, flier distribution through human resources departments, university list serves, community sites (churches, pharmacies, clinics) and a partnership with a local clinic serving primarily Latino patients so as to enhance generalizability.

Outcomes

Baseline participant characteristics are shown in Tables 1 (youth) and 2 (adults). Participants in each study group were similar with respect to age, gender, anthropometric measures, and

laboratory data. For both intervention versions there are two primary evaluation aims. The first is to determine if participation leads to weight loss in the participating high-risk mothers. While convincing evidence exists that a YMCA-based approach can result in weight loss consistent with that achieved in the DPP, it is not known whether the modifications in the curriculum proposed in this adaptation of the program will have a comparable result.³⁰ The primary outcome measure is the percent change in body weight at 6 months post-enrollment (2 months post-intervention) in adult participants. The second primary aim is to determine if participation results in youth having healthier weights and lifestyle habits. In youth, body mass index (BMI) standard deviation score and percent overweight will be measured. Secondary outcomes will include the same measures at 12 months. In addition, we are measuring changes in self-reported physical activity, dietary intake, measures of global health status and quality of life, change in blood pressure, and point-of-care laboratory test results including hemoglobin A1C and lipids. All outcomes are assessed at either participating YMCAs or an offsite location used for this purpose at the medical center. Finally, we seek to determine which approach is most cost effective with regard to costs associated with implementation, effectiveness for weight loss in adults, and longer-term utilization.

Statistical Analyses

The intention-to-treat principle will be used for all the analyses. Differences in participants' baseline characteristics and clinical outcomes between two groups were evaluated by a two-sample t-test test for continuous outcomes and by Chi-square test or Fishers Exact test for categorical outcomes. A mixed-model analysis of covariance including the terms, treatment group, time, gender, race, age, baseline value of body weight will be used to assess the effects of intervention at 6- and 12-month. Participants will be treated as a random effect and an un-structure covariance matrix will be used. An interaction effect between time and treatment group

will be assessed first. If there is no interaction effect, the overall treatment difference will be assessed. Otherwise, treatment difference will be assessed at each time point. In order to measure the relative cost-effectiveness of these programs, we will model the cost of each program using both explicit costs (such as salaries, rent, materials, etc.) and implicit costs (missed work time, societal improvements, etc.). Effectiveness will be measured through the study itself. When modeling cost-effectiveness, we will consider both the short (6 month) and longer-term (12 month) weight loss. For each treatment strategy, we will calculate the expected total costs by multiplying the probability of each unique outcome with its associated costs and then adding these values for all possible outcomes. For long-term outcomes, we will calculate total quality adjusted life years in adult participants (QALYs) for each treatment strategy. We will finally calculate the incremental cost-effectiveness of each strategy by dividing the difference in costs by the difference in QALYs. Finally, we will use a one-way sensitivity analysis to identify important model uncertainties.

Discussion and Conclusions

An urgent need exists for prevention initiatives that focus on lifestyle modification to be studied among youth and their families at highest risk for T2D. We have created a T2D risk-reducing curriculum (ENCOURAGE) for delivery to mothers who are at high-risk for developing T2D and who have school-aged children also at risk. The curriculum has been well-received by YMCA trained staff and study participants. We are now in the process of testing the ENCOURAGE programs.

Previous diabetes prevention trials in adults have been efficacy trials that gave little attention to the cost of implementing the program. These research-oriented programs are often unsuitable for dissemination in clinical settings, as the lifestyle modification program effectiveness is strongly correlated with program intensity and duration. Therefore, it is important to adapt evidenced-based curricula so that they can be delivered to a targeted

population in a cost effective manner. By testing two different interventions, we will be able to answer several questions that are crucial to developing an effective translation model: which approach results in the best outcomes, which is most liked by participants, and what are the costs associated with implementation? These data are essential to build a translation model of T2D prevention that is both realistic and feasible to address this growing national problem in both youth and adults.

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