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A comment on “Metformin in the Diabetes Prevention Program 3-year trial: The cost-effectiveness that never was”

William H. Herman, MD^{1,2}, Shihchen Kuo, PhD¹, Ping Zhang, PhD³ for the Diabetes Prevention Program Research Group

¹Division of Metabolism, Endocrinology, and Diabetes, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA

²Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA

³Division of Diabetes Translation, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

In their recent article in this journal,¹ Rittenhouse and Alolayan critiqued the Diabetes Prevention Program (DPP) Research Group’s 2003 article on the within-trial cost-effectiveness of lifestyle intervention or metformin for the primary prevention of type 2 diabetes.² They presented a primer on the various tools available for economic evaluations in 2024 and concluded that the research group’s decision to compare the DPP lifestyle intervention and metformin to placebo was inconsistent with current standards for the conduct of cost-utility analyses. Indeed, they argued that comparing both alternatives with placebo was inappropriate and led to incorrect conclusions.

The DPP was designed in the early 1990s, and its prospective economic evaluation was initiated over 30 years ago. Prior to the DPP, no randomized, controlled trial had rigorously studied a lifestyle intervention *and* a pharmacologic intervention, and it was challenging to assess and compare the resource utilization and costs of these very different approaches to type 2 diabetes prevention. When anticipating the translation of the DPP’s results into clinical practice, the research group recognized that some individuals with pre-diabetes might not tolerate metformin, some individuals might not have the time or motivation to engage in a lifestyle intervention, and some individuals might have strong preferences for one intervention or the other. For these reasons, the research group decided a priori to separately assess the effectiveness and cost-effectiveness of each intervention relative to the standard of care at the time, which was brief, annual lifestyle recommendations as provided to the DPP placebo group, rather than solely focusing on a head-to-head comparison of the lifestyle and metformin interventions.

Correspondence: William H. Herman, Diabetes Prevention Program Coordinating Center, George Washington University Biostatistics Center, 6110 Executive Blvd, Rockville, MD 20852, USA. dppmail@bsc.gwu.edu.

CONFLICT OF INTEREST STATEMENT

All authors are DPP/DPPOS investigators.

The research group also recognized that it was important to assess the cost-effectiveness of the interventions as they were implemented in the DPP and as they might be implemented in real-world clinical settings. The intensive lifestyle intervention was implemented one-on-one by a lifestyle care manager in part to speed the conduct of the trial. Branded metformin was used in the DPP as it was the only preparation of metformin available at the time. The study group performed additional analyses to assess the cost-effectiveness of a group lifestyle intervention, which it believed was likely to be the preferred model for implementation and which, based on the literature, was likely to be as effective if not more effective than an individually implemented lifestyle intervention due to the peer support provided by the group. It also performed analyses to assess the cost-effectiveness of generic metformin, which was soon to enter the US market. Some of the data used for these analyses, such as the cost of generic metformin, were based on our best estimate at the time, but proved to be substantially higher than the actual cost (\$1.10/tablet brand price vs. \$0.28/tablet estimated generic price vs. \$0.05/tablet current generic price). We did not anticipate that, given the choice, policymakers would opt for the more expensive and potentially less effective individual lifestyle intervention over a group lifestyle intervention, or branded metformin over an equally effective but substantially less expensive generic metformin. We therefore performed analyses to assess separately the cost-effectiveness of the DPP interventions as they were implemented in the clinical trial and as the research group anticipated they might be implemented in real-world clinical practice.

For these reasons, we chose not to use the efficient algorithm to sequentially rank the individual and group lifestyle interventions, the brand and generic metformin interventions, and the placebo intervention as performed by Rittenhouse and Alolayan in their re-analysis of our results. This type of analysis is typically done when interventions are clinically equivalent and competing, which we do not believe the DPP interventions were. Ultimately, the best intervention for type 2 diabetes prevention for an individual at high risk is likely to be the intervention that is effective and that they are willing to adopt.

Pre-specified analyses performed by the DPP research group showed that both the lifestyle and metformin interventions were effective and cost-effective compared with the placebo intervention. Over the ensuing years, subsequent analyses have addressed the effectiveness and cost-effectiveness of the interventions over longer time horizons. Two 10-year within-trial economic analyses^{3,4} and a simulated lifetime economic analysis⁵ bore out the research groups' original conclusions. Subsequent analyses performed by the DPP research group⁶ and others⁷ explored heterogeneity of treatment effect and benefit-based tailored treatment. These analyses demonstrated that metformin therapy was ineffective in preventing type 2 diabetes in participants at lowest risk but extremely effective for those at higher risk.^{6,7} A subsequent study using a microsimulation model demonstrated that although the metformin intervention was not cost-effective for patients in the lowest quintile of type 2 diabetes risk, it was cost-saving for those in the higher quintiles of risk.⁸ This study suggested that for patients at higher risk who were unable or unwilling to participate in the lifestyle intervention, prioritization of metformin therapy conferred value.⁸

Rittenhouse and Alolayan presented a useful primer on the current tools available to conduct cost-utility analyses. However, they did not account for the historical context of the DPP

and the nuances involved in comparing the cost-effectiveness of two novel, different, but effective interventions to the standard of care. This is especially true when considering translation of the results of the DPP into real-world clinical practice, where patients may have clear preferences for one intervention over the other. Although less effective, the cost of generic metformin is substantially lower than that of the lifestyle intervention. Furthermore, the metformin intervention, although ineffective in a small portion of the target population, was effective and indeed cost-saving in individuals at high risk for type 2 diabetes. We therefore maintain that both generic metformin and lifestyle intervention are cost-effective options when compared with the standard of care for prevention of type 2 diabetes in high-risk groups.

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DATA AVAILABILITY STATEMENT

In accordance with the NIH Public Access Policy, we continue to provide all manuscripts and letters to PubMed Central including this letter. DPP/DPPOS has provided the protocols and lifestyle and medication intervention manuals to the public through its public website (<https://www.dppos.org>). The DPPOS abides by the NIDDK data sharing policy and implementation guidance as required by the NIH/NIDDK (<https://www.niddkrepository.org/studies/dppos/>).

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