RESPONSE TO COMMENT ON CEFALU ET AL.

The Alarming and Rising Costs of Diabetes and Prediabetes: A Call for Action! Diabetes Care 2014;37:3137–3138

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Diabetes Care 2015;38:e82–e83 | DOI: 10.2337/dc15-0215

We thank Yudkin and Montori (1) for their letter in response to our editorial (2).

As outlined in the editorial, we feel a great deal of attention—perhaps too much—has been paid over the recent past to the fact that the ranges of impaired glucose tolerance, impaired fasting glucose, and A1C define different groups of people as being at risk, and that the individuals with dysglycemic levels at the lower ends of the glycemic ranges are at lower risk for progressing to diabetes than the individuals at the higher ends. We would agree that all of that has been well established. In fact, American Diabetes Association (ADA) guidelines expressly acknowledge these points, but we do not see the value in repeatedly and exhaustively making these observations. We can continue to argue over what the exact diagnostic cut points for each test should be, but the bottom line is that these are categories suggesting increased risk for developing diabetes, and it is inevitable that when you have physiological ranges of a continuous variable, the risks will be lower at the lower ends of the ranges than at the higher ends.

ADA's Standards of Care position statement (3) specifically acknowledges this differential risk for progression to overt diabetes, and the only "medicalization" called for in these patients is to say that metformin "may be recommended" specifically in those individuals at highest risk for progressing to diabetes—those who are obese, are younger than 60, or who have a history of gestational diabetes mellitus. For all others, ADA guidelines call for making at-risk individuals aware of their risk and encouraging lifestyle interventions to reduce that risk.

We believe that all of the recommendations are an appropriate reflection of the results of the Diabetes Prevention Program (DPP) and other studies and that the potential delay, not to mention possible prevention, of diabetes makes this intervention worthwhile. We believe that the article by Dall et al. (4) that started this discussion lends support to the value of intervention by showing that prediabetes itself involves an increased financial burden on individuals and the health care system. This is further supported by the prospective economic analysis of the DPP, demonstrating the cost-effectiveness of the lifestyle intervention and the cost-savings of metformin (5).

Yudkin and Montori (1) correctly observe that "metformin alone has not been shown to reduce the risk of diabetes-related complications." We are not arguing that point, but given the chronic time frame of both microvascular and macrovascular complications, no study is ever likely to demonstrate that metformin or any other individual agent will reduce the risk for complications. The natural history of type 2 diabetes almost always requires a succession of therapeutic agents to keep glucose levels in a healthy range, often culminating in a need for insulin. Given the knowledge we have today about the development of complications over the natural history of the disease, it would be unethical to leave a group of patients with type 2 diabetes on metformin alone for 20 years versus a control group on nothing to show that metformin reduced the risk for microvascular disease. But we have no doubt that it would do so, should such a trial ever occur.

In their commentary in *BMJ* (6), Yudkin and Montori observe that a downside of being diagnosed with diabetes includes "the need for medical care and treatment." It is on that very point that we disagree; we see it not as a downside, but as an upside. Being diagnosed with diabetes presents the *opportunity* to receive medical care and treatment, which has been repeatedly shown, most notably in the Diabetes Control and Complications Trial (DCCT) and UK Prospective Diabetes Study (UKPDS), to reduce the long-term risk of microvascular complications and perhaps even macrovascular disease.

We do believe in the medicalization of type 2 diabetes because we believe it represents a proven path to improved health and quality of life. Those demanding prospective randomized trials for cardiovascular end points before instituting any diabetes therapy must temper their demands by the ethical and practical aspects required for the

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study. A thoughtful analysis published earlier in *BMJ* (7) elegantly makes the case for why not every hypothesis can ethically be put to the test of a randomized controlled trial.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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