In Reply We thank Asensio-Sánchez for sharing his thoughts and appreciate the opportunity to respond to the comments. Asensio-Sánchez has accurately interpreted that this is the first time in the Diabetes Prevention Program Outcomes Study that age-related macular degeneration (AMD) assessment was performed; therefore, one cannot hypothesize on the prevalence or stage of AMD before the images were acquired.¹ The prevalence reported is for the current visit and does not account for previous time points. At the current visit, AMD was identified in 479 participants (30.0%) with early-stage AMD in 229 (14.4%), intermediate AMD in 218 (13.7%), and advanced AMD in 32 (2.0%). Breakdown by treatment arms is shown in Figure 2.

We concur with the authors’ comment on the crossover effect of metformin, which has also been discussed in detail in the article. We have carefully evaluated this potential confounder across all analyses. First, out-of-study metformin usage was collected from patients to the best possible extent and reported in the study. The mean number of years of any metformin use was 3.59 in the lifestyle arm and 4.35 in the placebo arm compared with 14.67 in the metformin arm. Although participants in the lifestyle and placebo arms also had taken metformin, the number of years exposed was significantly lower than the metformin arm.² Second, as shown in Table 2, the analysis for association of metformin with AMD was performed irrespective of the original study arm, which led to the study conclusions. Third, we classified the study population into those who had never used metformin and those who had used metformin, irrespective of number of years. As reported, the prevalence of AMD was 33.5% and 28.8%, respectively, further confirming the lack of association. Additionally, we analyzed the association between the type of metformin use (in-study vs out-of-study) and stage of AMD and found no association, as shown in Supplement 1.

Known risk factors for AMD, including age, sex, race, smoking status, BMI, and education level, were available and included.³,⁴ Medical history, family history, and genetic information were not included in the analysis. However, despite these limitations, the power of these analyses lies in the randomization of the cohort, intent-to-treat strategy, and the differences in the metformin usage in the different treatment arms over the long-term follow-up. The masked gradings for the different stages of AMD by a reading center is another strength. We acknowledge that these findings are different from other studies while also similar to others, reflecting the different methodologies and different data sets used to analyze the association of AMD and metformin use. The answer to this question lies in the prospective evaluation of metformin in a randomized clinical trial.