proteins. A few studies supported the evidence that not only dietary<br>but also physiologic exposures exhibit influences on δ-values of body<br>protein (5). However, it is probable that, in using natural stable iso-
tope signatures, the physiologic impact can only be uncovered by<br>measuring modifications of amino acid–specific δ-values. The pres-
etent study by Patel et al. (1) is based on bulk stable isotope measure-
ments in plasma protein, which does not allow for detailed amino<br>acid–specific interpretations. Although not yet often applied, amino<br>acid–specific nitrogen isotope composition analysis may help to dis-
tinguish factors related to dietary habits or disease states.

The author did not declare any conflicts of interest.

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Reply to KJ Petzke

Dear Editor:

We are pleased that Petzke appreciated our publication and found it positively noteworthy for a number of reasons, including its nov-
elty. Further to dietary explanations we advanced, he makes an in-
teresting additional suggestion of pathophysiologic processes for the interpretation of our divergent findings for the positive association between δ15N and incidence of type 2 diabetes and the inverse association with δ13C.

We agree, as argued by Petzke, that long-term pathophysiologic modifications of protein and amino acid metabolism among individu-
als with type 2 diabetes could affect stable isotope ratios of plasma<br>proteins (1–4). However, this is unlikely to have affected our findings to<br>a large extent, because in our study we analyzed stable isotopes in<br>baseline samples of nondiabetic individuals to investigate the asso-
ociation between isotopic values and incidence of (new-onset) type 2 diabetes, thus deliberately excluding those with known prevalent diabetes. Although some degree of potential misclassification of in-
dividuals with diabetes as nondiabetic is possible in large epidemi-
ologic studies such as ours, this would be relatively small.

We note, however, that the natural history of type 2 diabetes in-
cludes changes in glucose concentrations, insulin sensitivity, and in-
sulin secretion (5) as well as in lipids and transaminases (6) for some years before diagnosis, which our study was not set up to investigate.

There is a paucity of data investigating how pathophysiologic pro-
cesses affect isotopic fractionation in vivo, and a better understanding of the underlying processes is crucial to further develop applications for stable isotope ratios in nutritional epidemiology. Thus, it would indeed be of great interest to measure stable isotopes in studies with stored samples of repeat measures to advance this line of inquiry.

Moreover, as Petzke highlights, our research is currently based on<br>bulk stable isotope ratio measurements in human serum, which does not allow us to explore differences in amino acid metabolism, but we look forward to further research that can apply compound-specific amino acid isotope analysis (7, 8). Such data will help to distinguish and identify how factors related to dietary habits or disease states can affect the stable isotope distribution of serum proteins. Last, but not the least, the close relation between metabolism and isotopic frac-
tionation may not only be affected by dietary intake, phenotype, and disease state but probably also by differences in genotype, but to our knowledge this has not yet been studied. Investigating this association should also be a priority for future research into the application of stable isotopes in nutritional epidemiology.

It is encouraging that the publication of our work has generated new ideas for future research in this field, which we welcome.

None of the authors had a conflict of interest to declare.

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