# Reply to Klitz and Niklasson: Can viral infections explain the cross-sectional Austrian diabetes data?

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## Routes to Diabetes

The vast majority of diabetes patients suffer from type II diabetes. There are several theories for potential causes of its development, the most favored being the "exhaustion" of β-cells by chronic excess caloric intake combined with inactivity leading to obesity, diabetes, and cardiovascular disease (1). Viral infection could be a potential cause, however mainly for type I diabetes. Furthermore, autoimmunity might play a role in type I patients (2). A quotation from ref. 3 reads: "Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. . . . Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. . . . Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia." There are known monogenetic defects leading to maturity-onset diabetes of the young-type diabetes. In summary, there are several pathways leading to the same symptom: high glucose level. None of these paths exclusively explains the causality of the diabetes epidemic.

## Ljunganvirus

As discussed in Thurner et al. (4), viral infections can cause diabetes but cannot explain the peaks found in the Austrian population data as shown explicitly for influenza. We believe that this is also true for a zoonosis. The peaks point to a massive change of an external exposition. There is no rationale why a zoonosis should show a massive change in the entire population given the diverse range of environmental conditions, ranging from plains to mountains and humid to dry areas. Zoonoses, like tularemia or toxoplasmosis, show typical outbreaks of infections, which are localized and seasonal. No such outbreaks were reported in times that would correspond to the peaks in our report (4). Contrary to the argument in Klitz and Niklasson (5), it is unlikely that a zoonosis should affect a large proportion of the young population (if the infection happened after birth), or of the population of pregnant women.

## Discussion

An important lesson from ref. 4 is that not only excess caloric intake but also (massive) hypocaloric nutrition in a famine can lead to diabetes. The external exposure can only be detected when it occurs during a vulnerable time: pregnancy. Epigenetic changes may be responsible for this long-acting mechanism (6). This finding opens new opportunities for research because excess caloric intake and famine may address the same metabolic or epigenetic mechanisms. If such mechanisms can be identified, they could become targets for new therapeutic strategies. Important questions that remain are: Can such changes happen only in one direction? Or could external factors also reverse such changes if an intervention can be found to make the target "vulnerable" again?

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