

**Response to Drs. Simsek and de Boer**

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Response to Drs. Simsek and de Boer

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We thank Drs. Simsek and de Boer for their interest in our paper. We fully agree that in humans, the literature regarding the effects of azathioprine/6-mercaptopurine and methotrexate on fertility and reproduction in men is limited. As stated by Drs. Simsek and de Boer, the exact effects of thiopurines and methotrexate on paternally exposed children are poorly studied and several possible mechanisms are proposed. We would have preferred a longer follow-up time for children exposed to azathioprine/6-mercaptopurine or methotrexate, or even the possibility of following up the individuals

though adulthood. However, complete data on drug prescriptions have only been available from the nationwide prescription database maintained by the Danish Medicine Agency since January 1, 1995. We believe our length of follow up is reasonable with 25% of exposed children having a follow up period longer than 11.3 years for reporting long-term outcomes during childhood and adolescence. We agree that data on childhood infections and allergies would be very interesting but we were unable to gather this information since these diagnoses are not sufficiently valid in the Danish registries. To our knowledge, adverse vaccination reactions are not available in the Danish registries, and many adverse vaccination reactions might only be seen by the general practitioner (data that are not available). This is the first study of long-term follow up of children exposed to these immunomodulators and the results are reassuring for our selected outcomes. Our results should be confirmed in other settings.