Modeling the association between growth-based pubertal onset and the development of type 1 diabetes

Essi Syrjälä[1], Riitta Veijola[2,3], Harri Niinikoski[4,5,6,7], Jorma Toppari[4,5,7], Mikael Knip[8,9,10,11], Helena E. Virtanen[4], Jorma Ilonen[12,13], Suvi M. Virtanen[1,11,14,15], Jaakko Peltonen[16], Jaakko Nevalainen[1]

[1]Unit of Health Sciences, Faculty of Social Sciences, Tampere University, Tampere, Finland; [2]Department of Pediatrics, PEDEGO Research Unit, Medical Research Center, University of Oulu, Oulu, Finland; [3]Department of Children and Adolescents, Oulu University Hospital, Oulu, Finland; [4]Research Centre for Integrative Physiology and Pharmacology, Institute of Biomedicine, University of Turku, Turku, Finland; [5]Department of Pediatrics, Turku University Hospital, Turku, Finland; [6]Research Center of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland; [7]Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland; [8]Children's Hospital, Pediatric Research Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [9]Research Program for Clinical and Molecular Metabolism, Faculty of Medicine, University of Helsinki, Helsinki, Finland; [10]Folkhälsan Research Center, Helsinki, Finland; [11]Tampere Center for Child Health Research, Tampere University Hospital, Tampere, Finland; [12]Immunogenetics Laboratory, Institute of Biomedicine, University of Turku, Turku, Finland; [13]Clinical Microbiology, Turku University Hospital, Turku, Finland; [14]Department of Public Health and Welfare, Finnish Institute for Health and Welfare, Helsinki, Finland; [15]Tays Research, Development and Innovation Center, Tampere University Hospital, Tampere, Finland; [16]Faculty of Information Technology and Communication Sciences, Tampere University, Tampere, Finland

Contact: Essi Syrjälä, essi.syrjala@tuni.fi

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Abstract

The incidence of type 1 diabetes (T1D) has increased worldwide with Finland having the highest rates[1] but reasons for the increase remains still unclear. The studies concerning the association between pubertal onset and T1D are lacking. Since there occur various changes in body during puberty it could potentially affect to the T1D development.

We set out to 1) determine the ages at pubertal onset based on growth, and 2) develop a model to study the association between growth-based pubertal onset and the development of T1D and related antibodies, with consideration of measurement error included in pubertal onsets, and different forms of effect.

The Type 1 Diabetes Prediction and Prevention (DIPP) birth cohort included follow-up for growth, T1D and related antibodies until the age of 15 years. The data from two other Finnish cohort studies, Special Turku Coronary Risk Factor Intervention Project and the Boy cohort, were used to construct the pubertal onset prediction model since those cohorts included not only follow-up for growth but also for pubertal development. Prediction model was used to obtain the growth-based pubertal onsets with prediction intervals for the DIPP children. Multi-state model[2] was used to study the association between growth-based pubertal onset and the development of T1D and related antibodies among DIPP.

Multiple imputation was used to consider an error included in the predictions: individual pubertal onset timings were randomly derived from the individual prediction intervals multiple times. Shape and duration of the pubertal onset effect were chosen as data-driven by investigating the several alternative options. Pubertal onset effects were incorporated into a multi-state model by using appropriate functions, and performance of the modeling was assessed with simulations.

Growth-based pubertal onsets should be interpreted as intervals rather than point estimates. Multiple imputation enabled the utilization of prediction intervals in consideration of the measurement error. Simulations showed that multi-state models with incorporated pubertal onset functions succeeded.

References

1. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. *The Lancet*. 2014;383(9911):69-82.

2. Van Den Hout A. *Multi-state survival models for interval-censored data.* CRC Press; 2016.