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Lancet Editor

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Dear Sir or Madam:

Thomas et al in the Lancet (1) describe the substantial proportion of adult-onset diabetes patients in UK Biobank with high type 1 diabetes (T1D) gene risk scores, progression to insulin therapy and, adult-onset disease. We believe additional issues should be considered which would change the conclusion without changing the evidence.

The authors have assumed genetic homogeneity across the broad age range of T1D but their T1D genetic risk score in UK Biobank individuals is defined by childhood-onset T1D. This gene risk score does not take into account the attrition of HLA and genetic risk reflected in loss of HLA-DQ6.2, HLA heterozygosity and twin concordance rates (2,3,4, 5). The authors allowed for this protective genetic effect in their analysis, but only using gene risk scores based on childhood-onset T1D; therefore, by sacrificing sensitivity for specificity, they underestimate the frequency of adult-onset T1D in this cohort.

In the Box, which accompanies the article, it is suggested that in adults, T1D is rare (2-5% of all diabetes patients) (1). In making this estimate they likely assume that all T1D patients are initially insulin-dependent, not consistently part of the T1D definition. Indeed, in their paper genetically defined T1D (representing 22% of the group eventually requiring insulin treatment) showed a proportion, which did not require insulin one year post-diagnosis (1,2,3,4).

Finally, they suggest that 1-7% of type 2 diabetes cases will have false positive autoantibodies based on a suggestion that 1-7% of normal individuals have positive autoantibodies. Apart from values for control autoantibody positivity being high they conflate that percentage in controls with percentage in diabetes patients not initially insulin- requiring. Both analyte specificity and positive predictive values increase as you enrich the at-risk population. The formula for a positive predictive value (PPV) reflects that effect:

$$PPV = \frac{sensitivity \times prevalence}{sensitivity \times prevalence + (1 - specificity) \times (1 - prevalence)}$$

When selecting cases to enrich cohorts of interest in series: 1) adult-onset diabetes, 2) initially non-insulin requiring, and 3) analyte specificity, such as diabetes-associated autoantibodies, both analyte specificity and positive predictive values, are likely much higher than the authors imply (1,3,4). By selecting cases with adult-onset diabetes, the authors increased the specificity of their genetic risk score but failed to capture the marked non-genetic effect reflected in their low Hazard Ratio (1.23) (1, 2, 3, 4, 5). In summary, they underestimate the proportion of cases with adult-onset autoimmune T1D (2,3,4,5). Analysing both autoantibodies and adjusted gene risk scores in this and other cohorts should be informative.

With best wishes

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References

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