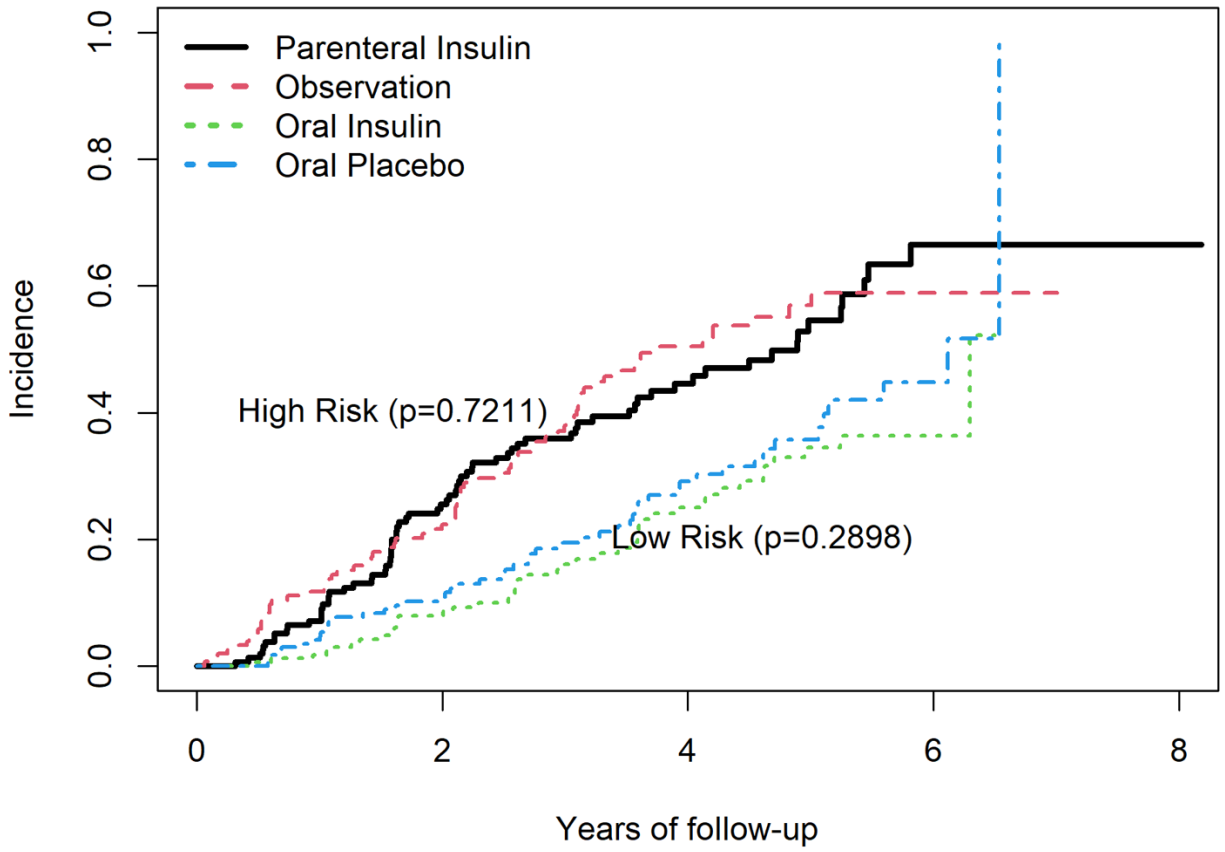
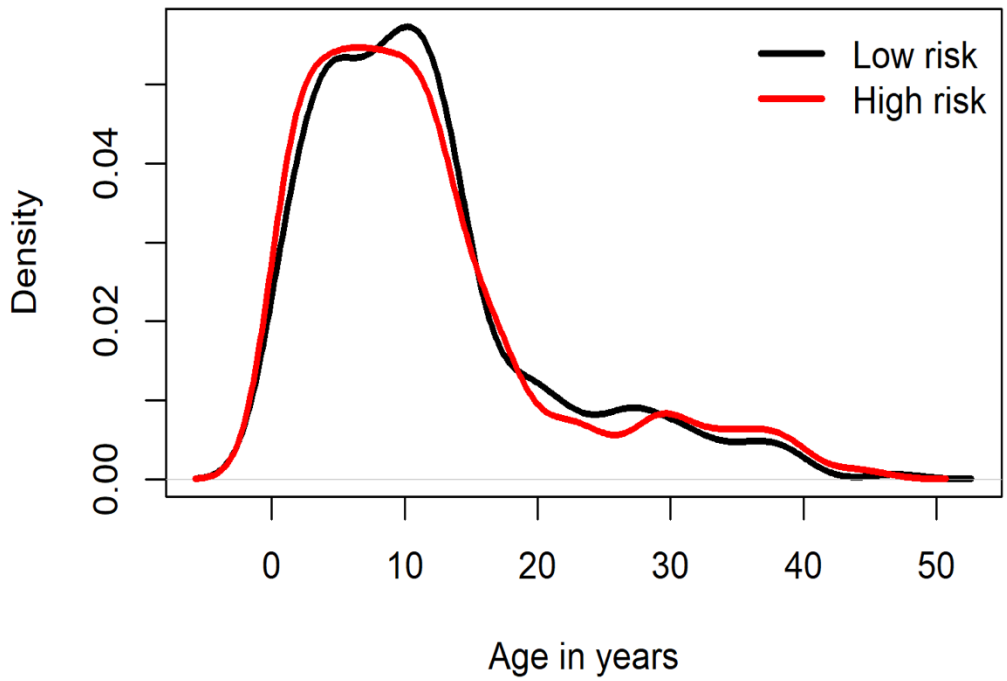
SUPPLEMENTARY FIGURES

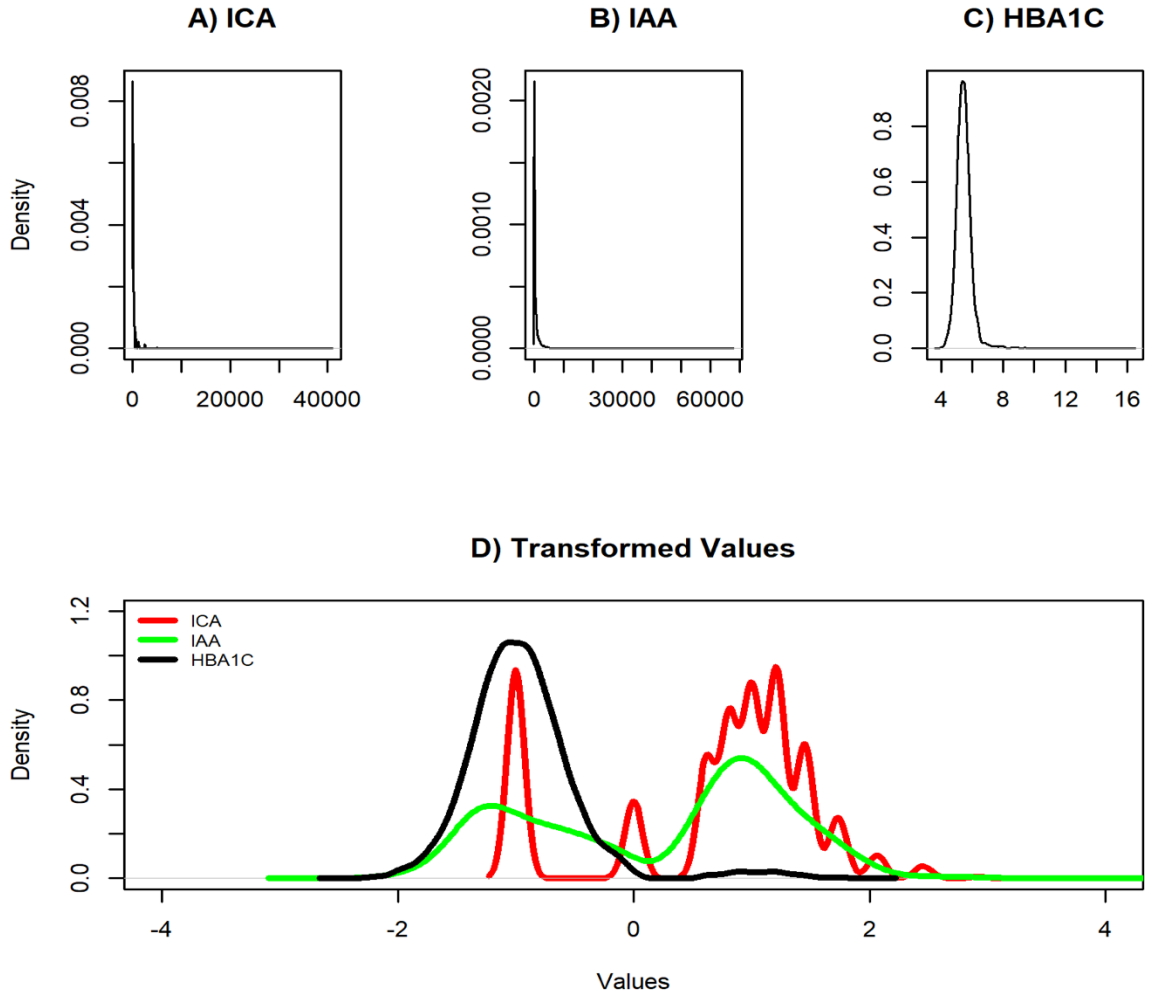
Supplementary Figure S1. Incidence curves of participants in four trial groups: high risk subjects were randomized to parenteral insulin (n=159) and observation (n=157), and low risk subjects were randomized to oral insulin (n=177) and oral placebo (n=177).



Supplementary Figure S2. Distributions of participants' ages among those with low and high risk for type 1 diabetes.

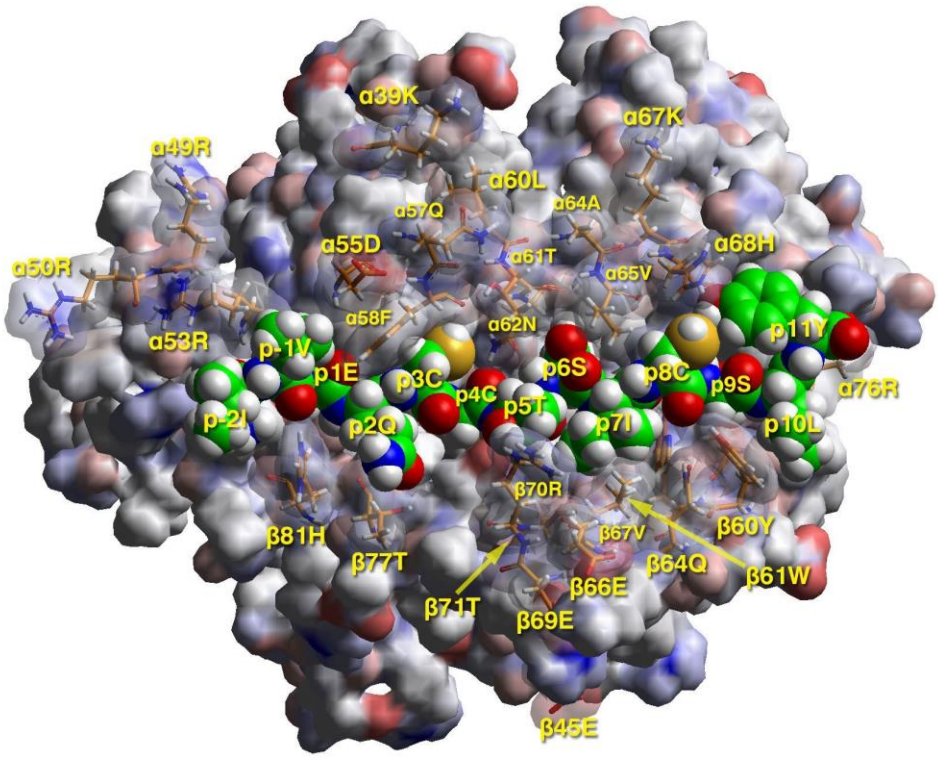


Supplementary Figure S3. Density distribution of original biomarker levels (ICA, IAA and HbA1c in the top three panels), and their transformed values by bi-directional power transformation (three lines in panel D).



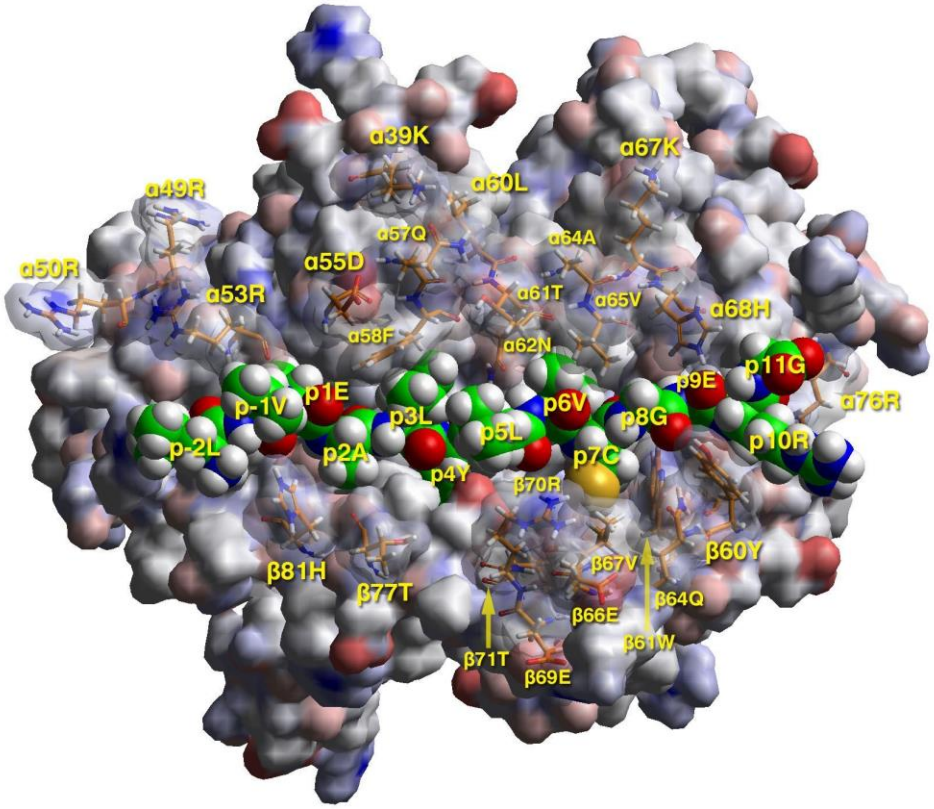
Supplementary Figure S4**.** The HLA Class II beta chain residue β57 is the determinant of many important structural and biological properties of the HLA-DQ heterodimer. We provide an example of each of the two haplotypes HLA-DQ7 (A1*03:01-B1*03:01), and HLA-DQ8 (A1*03:01-B1*03:02). For simplicity, only the α1β1 (antigen-binding) domain of HLA-DQ8 is shown, where select surface residues shown potentially interact with associated TCRs along with the bound insulin peptide (different in each case).

Supplementary Figure S4A



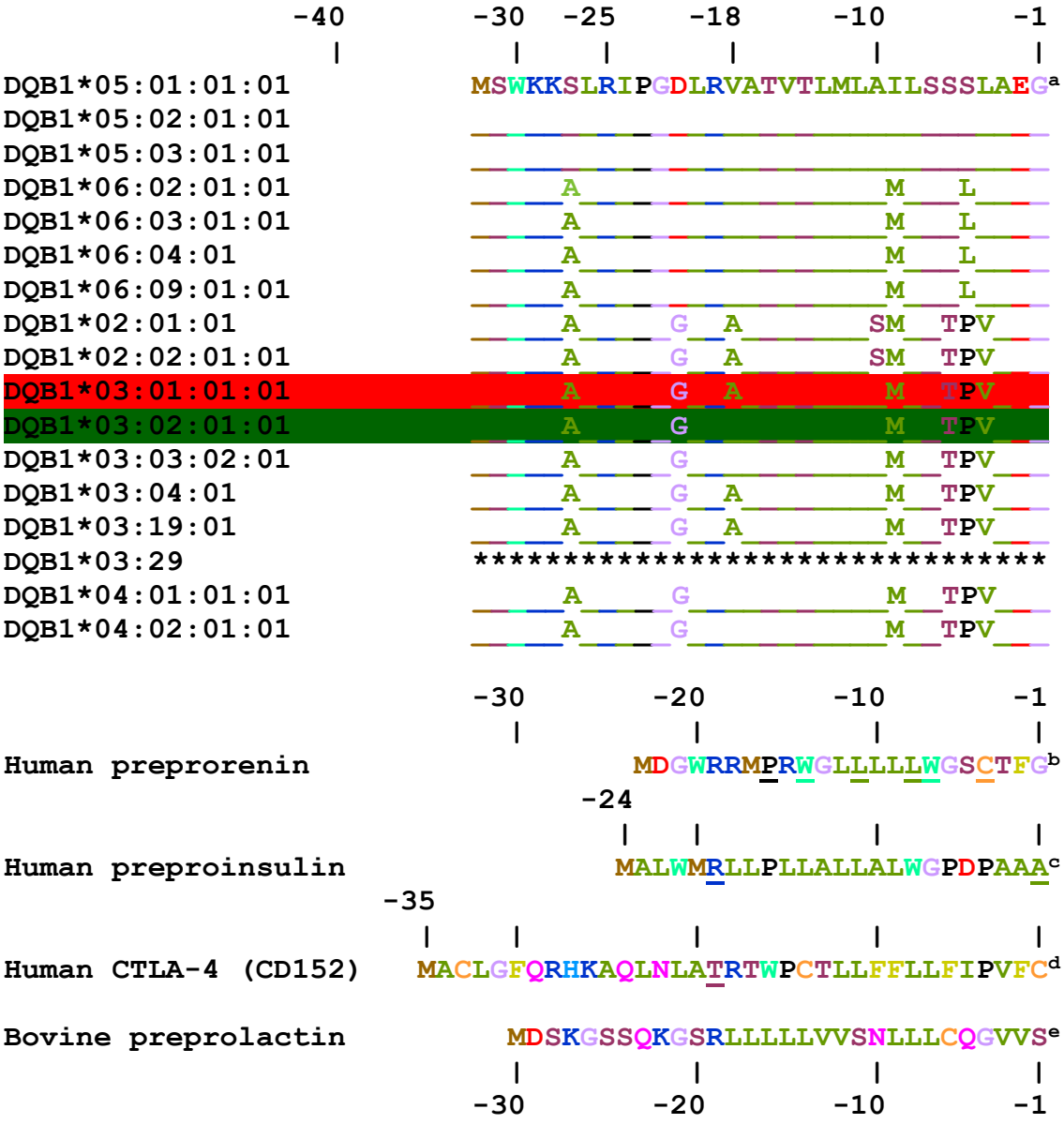
A. TCR view of the modelled structure of the HLA-DQ7—InsA2-14 with the α1β1 domain depicted as surfaces according to atomic charge (positive, blue; negative, red; neutral, grey; partial positive or negative charges with shades in-between), select HLA-DQ7 residues that are potential TCR contacts in stick form (nitrogen, blue; oxygen, red; carbon, orange; sulfur, yellow; hydrogen white) with transparent surface, and the bound antigenic peptide in space-filling form (same atom convention except carbon that is green). Residue β57Asp is opposite to α76Arg covered by pocket 10 Leu (p10Leu). Also shown is β45Glu/Gly in HLA-DQ7/DQ8 that affects considerably the surface electrostatic potential of the complex, and thus TCR selection (62).

Supplementary Figure S4B



B. TCR view of the structure of the HLA-DQ8—InsB11-23/24Gly complex (1jk8.pdb) as reported (42). Residue β57Ala is under p10Arg, while α76Arg forms a salt bridge with the side-chain carboxylate of p9Glu (partly covered). Evidence has been presented that during TCR interaction the InsB11-23 peptide is bound in the B14-B22 core nonamer register, yet the crystal structure shows the InsB13-B21 as the core bound nonamer (42, 63). Same depiction and color conventions as in A. Note the different anchors at p4, p6, p7 and p9 in HLA-DQ7, compared to HLA-DQ8, while the p1 anchor is the same, because of essentially identical pockets.

Supplementary Figure S5. Amino acid signal peptide sequences of HLA-DQB molecules, human preprorenin, preproinsulin, and CTLA-4, and bovine preprolactin.



Notes:

a. Coloring system from Papadopoulos GK et al. "A simplified system for coloring residues in amino acid sequences according to their physicochemical properties", *in preparation*. The DQB1*03:01 allelic sequence is shaded red ("preventive" for T1D development), while the DQB1*03:02 allelic sequence is shaded green ("permissive" for T1D development).

b. Naturally occurring mutations underlined. Information on the mutations obtained from (57).

c. Naturally occurring mutations underlined. Information on the mutations obtained from (58).

d. Naturally occurring mutation underlined. Information on the mutations obtained from (59).

e. Three-dimensional structure of biosynthetic intermediate analyzed in (47).

COLOR CODE FOR AMINOACID RESIDUES:

Based on nitrogen being blue, oxygen being red, and hydrophobic residues resembling olive oil.

D, E, acidic, COO^-

R, K, basic, $[-HN=C-(NH_2)_2]^+$, NH_3^+

H, histidine, aromatic, acidic-basic properties of imidazole ring

Q, N, polar, amide side group $O=C-NH_2$

W, H-bond donor N-containing indole ring, aromatic

Y, H-bond donor OH-containing, aromatic

S, T, OH-containing, H-bond donor, amphiphilic

F, aromatic, hydrophobic

A, V, I, L, aliphatic, hydrophobic

C, sulfur-containing, slightly hydrophilic, potential S-S bond former

M, sulfur-containing, hydrophobic

G, glycine, most flexible

P, proline, breaks continuity of α-helix, β-sheet