Elevations in blood glucose before and after the appearance of islet autoantibodies in children

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Supplemental Table 1. Visit age and mean non-fasting pre- and post-prandial blood glucose values

Visit	N children with glucose measurement	Age at visit; Median (Min – Max) (years)	Mean pre-prandial glucose concentration (mg/dl (mmol/L))	Mean 30 min. post prandial glucose concentration (mg/dl(mmol/L))	Mean 60 min. post prandial glucose concentration (mg/dl (mmol/L))
Visit 1	1,038	0.51 (0.33 – 0.59)	92.6 (5.14)	105.0 (5.83)	100.8 (5.60)
Visit 2	1,014	0.67 (0.48 – 0.80)	90.6 (5.03)	104.8 (5.82)	99.0 (5.50)
Visit 3	1,003	0.83 (0.64 – 0.99)	89.1 (4.95)	103.0 (5.72)	98.4 (5.47)
Visit 4	911	1.16 (0.94 – 1.34)	88.7 (4.93)	99.6 (5.53)	96.9 (5.38)
Visit 5	775	1.50 (1.39 – 1.69)	88.1 (4.89)	-	-
Visit 6	590	1.99 (1.75 – 2.21)	89.4 (4.97)	-	-
Visit 7	354	2.49 (2.41 – 2.73)	90.4 (5.02)	-	-
Visit 8	194	3.00 (2.94 – 3.17)	91.4 (5.08)	-	-
Visit 9	73	3.46 (3.39 – 3.60)	92.6 (5.14)	-	-

Supplemental Table 2. SNPs and their respective weights used to calculate the glucose GRS

SNP	Risk allele	Nearest gene	Allele Weight
Rs340874	C	PROXI	0.439
Rs11071657	A	FAM148B	0.270
Rs11558471	A	SLC30A8	0.911
Rs4506565	T	TCF7L2	0.885
Rs560887	C	G6PC2	2.532
Rs10830963	G	MTNR1B	2.262
Rs4607517	A	GCK	2.093
Rs2191349	T	DGKB/TMEM195	1.013
Rs780094	C	GCKR	0.979
Rs11708067	A	ADCY5	0.911
Rs7944584	A	MADD	0.709
Rs10885122	G	ADRA2A	0.743
Rs174550	T	FADS1	0.574
Rs11605924	A	CRY2	0.506
Rs11920090	T	SLC2A2	0.675
Rs7034200	A	GLIS3	0.608

SNP, single nucleotide polymorphism; GRS, genetic risk score

Table 3. Multivariate linear regression analysis (site-harmonized glucose measurements, adjusted for visit age)

	Visit 1 – Visit 4 (age 4 months – 1.35 years)				Visit 5 – Visit 7 (age 1.4 years – 2.7 years)			
Variable	N observations	N children	Estimate [95% CI]	P-value	N observations	N children	Estimate [95% CI]	P-value
Gender	2,835	751			1,182	559	Not included	-
Female	1,419	373	Reference	-	619	285		
Male	1,416	378	1.2 [0.3; 2.1]	0.0099	563	274		
BMI	2,835	751	0.4 [0.1; 0.7]	0.0029	1,182	559	Not included	-
Glucose GRS	2,835	751	0.2 [0.1; 0.4]	0.0016	1,182	559	0.4 [0.2; 0.7]	0.0011
Any islet autoantibodies	2,835	751	Not included	-	1,182	559		
No	2,662	706			1,105	521	Reference	
Yes	173	45			77	38	4.30 [1.2; 7.2]	0.006
INS genotype	2,835	751			1,182	559	Not included	-
AA	1,603	425	-1.4 [-2.3; -0.5]	0.0017	652	317		
other	1,232	326	Reference		530	242		

BMI Body Mass Index, GRS Genetic Risk Score, INS Insulin

Supplemental Table 4**.** Multivariate linear regression analyses (site-harmonized glucose measurements, adjusted for visit age) of post prandial glucose values at 30 min after food intake

	Visit 1 – Visit 4 (age 4 months – 1.35 years)			
Variable	N observations	N children	Estimate (95% CI)	P-value
Sex	2,544	747		
Female	1,249	370	Reference	–
Male	1,295	377	2.4 (1.1; 3.6)	0.0002
Glucose GRS	2,544	747	0.3 (0.1; 0.5)	0.003
Any islet autoantibodies	2,544	747		
No	2,429	715	Reference	
Yes	115	32	5.4 (2.4; 8.4)	0.0004

CI, confidence interval; GRS, genetic risk score;

Supplemental Table 5. Univariate linear regression analyses (site-harmonized pre-prandial glucose measurements, adjusted for visit age): sensitivity analysis excluding data from UK and Sweden.

	Visit 1 – Visit 4				Visit 5 – Visit 9*			
Variable	N observations	N children	Estimate (95% CI)	P-value	N observations	N children	Estimate (95% CI)	P-value
Sex	3,124	826			1,609	620		
Female	1,566	412	Reference	–	847	314	Reference	–
Male	1,558	414	1.4 (0.7; 2.1)	<0.0001	762	306	1.1 (−0.2; 2.4)	0.085
First degree relative with T1D	3,124	826			1,609	620		
No	1,348	355	Reference	–	612	258	Reference	–
Mother	753	199	0.7 (−0.2; 1.6)	0.14	427	156	0.9 (−0.7; 2.5)	0.27
Other	1,023	272	1.0 (0.2; 1.9)	0.012	570	206	−0.8 (−2.3; 0.7)	0.28
BMI	3,121	826	0.6 (0.4; 0.8)	<0.0001	1,605	620	0.8 (0.3; 1.2)	0.00051
Glucose GRS	2,233	588	0.2 (0.1; 0.3)	0.0040	1,069	433	0.4 (0.1; 0.6)	0.0066
Any islet autoantibodies	3,124	826			1,360	620		
No	2,882	763	Reference		1,235	566	Reference	
Yes	242	63	−0.1 (−1.4; 1.3)	0.91	125	54	2.2 (−0.1; 4.5)	0.059
Multiple islet autoantibodies	3,124	826			1,360	620		
No	2,952	781	Reference		1,269	583	Reference	
Yes	172	45	0.1 (−1.5; 1.6)	0.93	91	37	3.0 (0.3; 5.7)	0.028
***INS* genotype**	3,124	826			1,609	796		
AA	1,756	463	−1.1 (−1.8; −0.4)	0.0024	892	352	0.2 (−1.1; 1.5)	0.77
other	1,368	363	Reference		717	268	Reference	

CI, confidence interval; T1D, type 1 diabetes; BMI, body mass index; GRS, genetic risk score; *INS*, *Insulin* gene

Supplemental Table 6. Univariate linear regression analyses (site-harmonized glucose measurements, adjusted for visit age): sensitivity analysis using pre-prandial glucose values at visit 1 only

	Visit 1 (Age 4 – 7 months)		
Variable	N observations	Estimate (95% CI)	P-value
Sex	1,038		
Female	511	Reference	–
Male	527	1.8 (0.4; 3.2)	0.013
First degree relative with T1D	1,038		
No	489	Reference	–
Mother	231	−0.73 (−2.6; 1.1)	0.44
Other	318	0.05 (−1.6; 1.7)	0.94
BMI	1,038	1.1 (0.7; 1.5)	<0.0001
Glucose GRS	743	0.2 (−0.1; 0.5)	0.17
Any islet autoantibodies	1,038		
No	966	Reference	
Yes	72	−0.2 (−3.1; 2.6)	0.88
Multiple islet autoantibodies	1,038		
No	985	Reference	
Yes	53	0.5 (−2.7; 3.8)	0.76
***INS* genotype**	1,038		
AA	580	−2.3 (−3.8; −0.9)	0.0016
other	458	Reference	

CI, confidence interval; T1D, type 1 diabetes; BMI, body mass index; GRS, genetic risk score; *INS, Insulin* gene

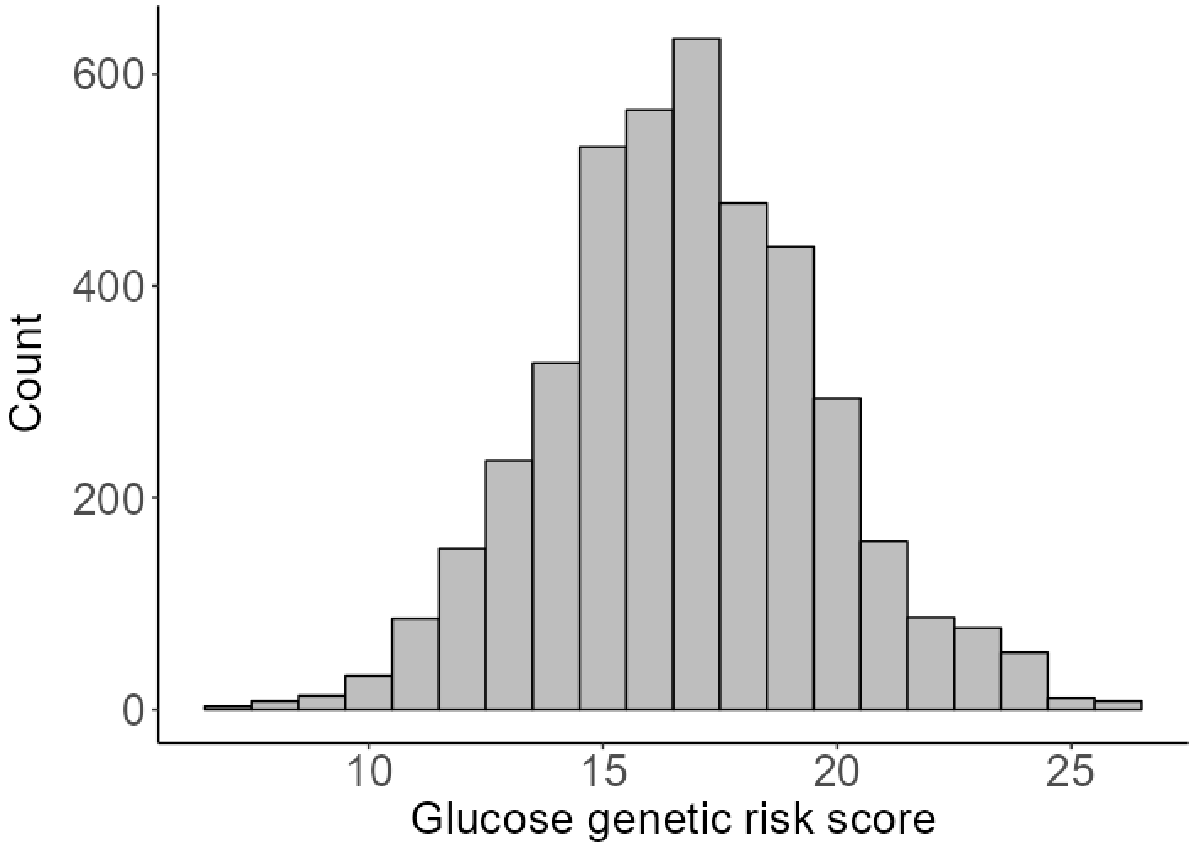
Supplemental Table 7: List of SNPs used to determine study eligibility and risk score calculation

SNP	Gene, Allele, or Haplotype	Score weight for genotype or per allele
HLA class II		
rs17426593	HLA DR4-DQ8/DR4-DQ8	3.15
rs2187668		3.98
rs7454108	HLA DR3/DR4-DQ8	
rs3129889	HLA *DRB1**1501	Exclusion criteria for first degree relatives
rs1794265	HLA *DQB1**0503	Exclusion criteria for first degree relatives
HLA class I		
rs1264813	HLA A 24	0.43
rs2395029	HLA B 5701	0.92
Non-HLA SNPs		
rs2476601	*PTPN22*	0.76
rs2816316	*RGS1*	0.16
rs3024505	*IL10*	0.22
rs1990760	*IFIH1*	0.16
rs3087243	*CTLA4*	0.16
rs10517086	*C4orf52*	0.19
rs2069763	*IL2*	0.11
rs6897932	*IL7R*	0.19
rs3757247	*BACH2*	0.19
rs9388489	*C6orf173*	0.14
rs6920220	*TNFAIP3*	0.15
rs1738074	*TAGAP*	0.05
rs7804356	*SCAP2*	0.15
rs4948088	*COBL*	0.17
rs7020673	*GLIS3*	0.23
rs12722495	*IL2RA*	0.47
rs947474	*PRKCQ*	0.15
rs10509540	*RNLS/C10orf59*	0.25
rs689	*INS*	0.65
rs4763879	*CD69*	0.06
rs2292239	*ERBB3*	0.36
rs3184504	*SH2B3*	0.24
rs1465788	*ZFP36L1*	0.13
rs17574546	*RASGRP1*	0.13

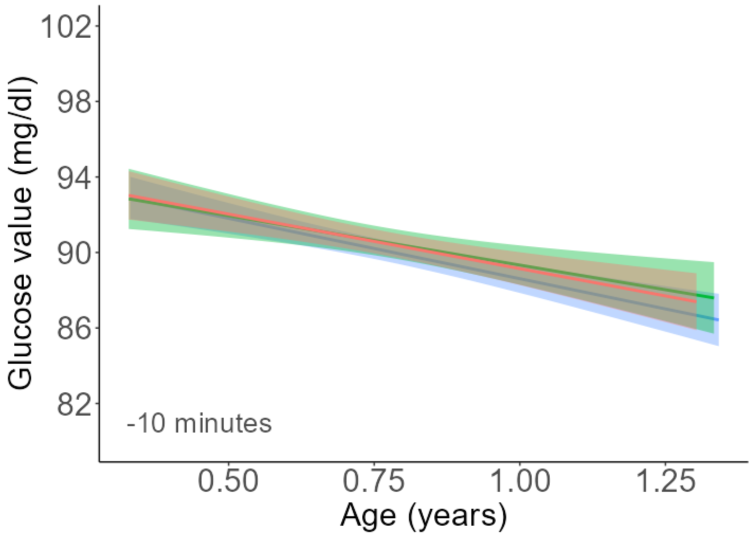
rs3825932	*CTSH*	0.15
rs12708716	*CLEC16A*	0.15
rs4788084	*IL27*	0.20
rs7202877	*CTRB2*	0.19
rs2290400	*ORMDL3*	0.25
rs7221109	*CCR7*	0.15
rs45450798	*PTPN2*	0.09
rs763361	*CD226*	0.12
rs425105	*PRKD2*	0.21
rs2281808	*SIRPG*	0.07
rs3788013	*UBASH3a*	0.16
rs5753037	*RPS3AP51*	0.15
rs229541	*IL2B*	0.18
rs5979785	*TLR8*	0.09
rs2664170	*GAB3*	0.14

The risk score is calculated by multiplying the number of risk alleles (i. e. 0, 1 or 2 for each single SNP) with the weight assigned to each SNP and then summing up the weighted contributions of all SNPs plus an additive constant of 3.15 for infants who have the HLA DR4-DQ8/DR4-DQ8 genotype or 3.98 for infants who have the HLA DR3/DR4-DQ8 genotype. As an example, the risk score for a child with HLA DR4-DQ8/DR4-DQ8, homozygous for the risk allele of rs1264813 (weight 0.43), heterozygous for the risk allele of rs2395029 (weight 0.92), homozygous for the non-risk allele of rs2476601 (weight 0.76) and for all other SNPs in the genetic risk score is calculated as follows:

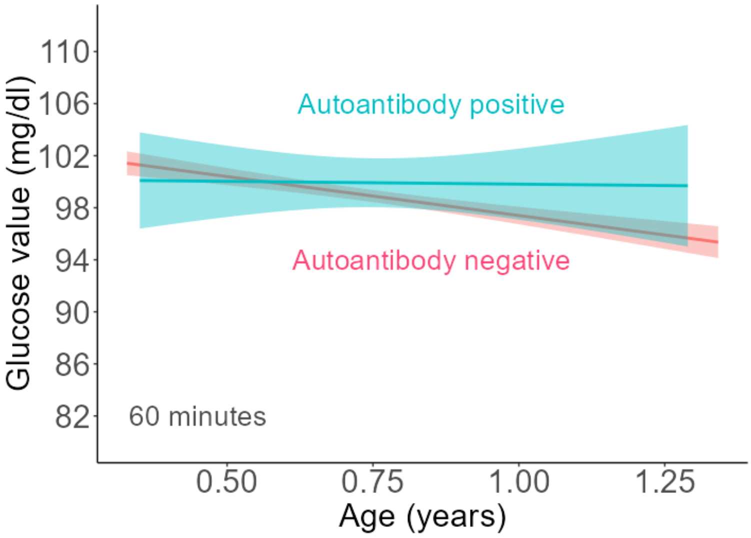
Risk score = 3.15 + (2 * 0.43) + (1 * 0.92) + (0 * 0.76) + 0 = 4.93



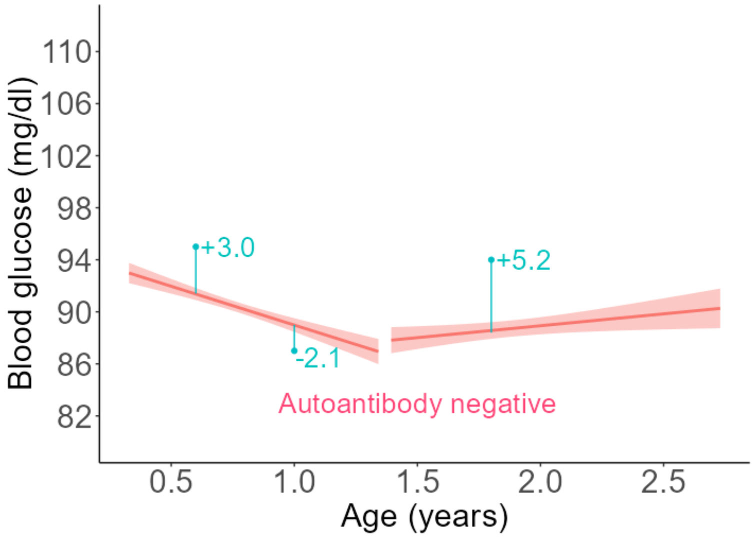
Supplemental Figure 1. Histogram showing the distribution of the glucose genetic risk score (count of measurements for each unit of score).



Supplemental Figure 2. Linear regression of pre-prandial glucose values by visit age in the infancy period (visits 1–4; 4 months–1.35 years of age) according to the child's first-degree relative status: none (blue), mother (green), and other (red).



Supplemental Figure 3. Linear regression of post-prandial glucose values (60 min after food intake) by visit age in the infancy period (visits 1– 4; 4 months–1.35 years of age) for islet autoantibody-positive (blue) and islet autoantibody-negative (red) children.



Supplemental Figure 4. Schematic of the method used to calculate the differences in glucose values in autoantibody positive children (blue points) from the linear regression curves of glucose values in autoantibody negative-children (red)

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