

ESM Table 1: Type 1 diabetes studies evaluating the impact of age at diagnosis on the genetic risk for type 1 diabetes. The highest risk HLA genotype (DR3-DQ2/DR4-DQ8) and protective haplotype (DR15-DQ6) are reported. No upper age was reported if not stated. Where statistical comparisons between age groups were not stated in the original study Chi-squared test was used to compare age groups by HLA status. ^ p value reported for change in odds ratio with increasing onset age.

Study (reference)	How type 1 diabetes defined	Ages studied (n)		Genetic associations with increasing age			
		Younger age group	Older age group	DR3-DQ2/DR4-DQ8 (Younger vs Older)	p	DR15-DQ6 (Younger vs Older)	p
Karjalainen et.al (1989) (1)	Clinician Diagnosed	≤18 years (82)	>18 to 56 years (44)	37% (26 to 47%) vs 13% (2 to 23%)	0.01	Not Reported	N/A
Caillat-Zucman et.al (1992) (2)	Clinician Diagnosed	<15 years (112)	≥15 years (290)	38% (29 to 46%) vs 18% (14 to 22%)	<0.0001	3% (0 to 6%) vs 5% (2 to 7%)	0.4
		15-30 years (183)	>30 years (107)	24% (18 to 30%) vs 10% (5 to 16%)	<0.01	Not Reported	N/A
Vandewalle et.al (1993) (3)	Clinician Diagnosed	≤19 years (126)	20 to 39 years (153)	40% (31 to 48%) vs 20% (14 to 26%)	<0.001	Not Reported	N/A
Tait et.al (1995) (4)	Clinician Diagnosed & C-peptide <0.1nm	≤20 years (115)	>21 years (79)	48% (39% to 57%) vs 29% (19 to 39%)	<0.01	3% (0 to 8%) vs 8% (0 to 18%)	0.2
Graham et.al (1999) (5)	Clinician Diagnosed	≤20 years (566)	≥20 to 34 years (264)	33% (30 to 37%) vs 24% (19 to 29%)	0.02^	1% (0 to 2%) vs 3% (2 to 7%)	<0.001^
Sabbah et.al (2000) (6)	Clinician Diagnosed	<20years (188)	≥20 to 62 years (59)	23% (17 to 29%) vs 8% (1 to 16%)	0.01	2% (0 to 3%) vs 10% (2 to 18%)	<0.01
Petrone et.al (2005) (7)	Clinician Diagnosed	<15 years (650)	≥15 to 49 years (221)	24% (21 to 27%) vs 14% (9 to 19%)	<0.01	Not Reported	N/A
Howson et.al (2011) (8)	Clinician Diagnosed & ≥1 autoantibody	3 to ≤21 years (325)	>21 to 89 years (944)	23% (18 to 27%) vs 20% (17 to 22%)	0.2	2% (0 to 3%) vs 4% (3 to 6%)	0.02
Thomas et.al (2022) (9)	Clinician Diagnosed & ≥1 autoantibody	<18 years (n=642)	≥18 (n=894)	28% (25 to 32%) vs 19% (16 to 22%)	<0.0001	2% (1 to 3%) vs 3% (2 to 4%)	0.1

ESM Table 2. Studies evaluating the impact of age at diagnosis on percentage of type 1 diabetes cases islet autoantibody positive. [^] Autoantibodies tested within 1 year of diagnosis, ^{^^} Autoantibodies tested within 2 years of diagnosis. No upper age was reported if not stated. Where statistical comparisons between age groups were not stated in the original study Chi-squared test was used to compare autoantibody status between age groups.

Study	Type 1 diabetes definition	Autoantibodies measured	Ages studied		autoantibodies reported	Antibody positive		P
			Younger age group	Older age group		Children	Adults	
Lohmann et.al (1997) (10) ^{^^}	Clinician Diagnosed	ICA, GADA, IA-2A	12-40 years (22)	>40-67 years (24)	≥1 Ab +ve GADA	83% (67 to 98) 74% (60 to 95)	58% (39 to 78) 29% (11 to 47)	0.07 <0.01
Sabbah et.al (2000) (6) [^]	Clinician Diagnosed	ICA, IAA, GADA, IA-2A	<20 years (252)	≥20-62 years (100)	≥1 Ab +ve GADA ≥2 Ab +ve	96% (94 to 98) 68% (62 to 74) 70% (64 to 76)	70% (61 to 79) 51% (41 to 61) 34% (25 to 43)	<0.0001 <0.01 <0.001
Vermeulen et.al (2011) (11) [^]	Clinician Diagnosed	GADA, IA-2A, ZNT8	≤19 years (393)	>19-40 years (262)	≥1 Ab +ve ≥2 Ab +ve	94% (92 to 97) 73% (68 to 77)	79% (74 to 84) 53% (47 to 59)	<0.0001 <0.0001
Bravis et.al (2018) (12) [^]	Clinician Diagnosed	GADA, IA-2A, ZNT8	<17 years (676)	≥17 years (1102)	≥1 Ab +ve	90% (88 to 92)	82% (80 to 84)	<0.0001
Rogowicz-Frontczak et.al (2018) (13) [^]	Clinician Diagnosed	ICA, GADA, IA-2A, ZNT8	<35 years (66)	≥35 years (53)	≥1 Ab +ve GADA ≥2 Ab +ve	92% (86 to 99) 82% (72 to 91) 88% (80 to 96)	85% (75 to 95) 77% (66 to 89) 55% (41 to 68)	0.2 0.5 <0.0001
Niechcial et.al (2018) (14) [^]	Clinician Diagnosed	GADA, IA-2A, ZNT8	<18 years (218)	≥18 years (149)	≥1 Ab +ve GADA ≥2 Ab +ve	95% (92 to 98) 87% (83 to 92) 70% (64 to 76)	81% (75 to 87) 49% (41 to 57) 74% (67 to 81)	<0.0001 <0.0001 0.3
Luo et.al (2020) (15) ^{^^}	Clinician Diagnosed	GADA, IA-2A, ZNT8	≤20 years (340)	>20-70 years (411)	≥1 Ab +ve GADA ≥2 Ab +ve	76% (71 to 82) 61% (54 to 67) 39% (33 to 46)	63% (57 to 69) 57% (51 to 63) 24% (19 to 29)	<0.01 0.4 <0.001
Thomas et.al (2022) (9) [^]	Genetic stratification	GADA, IA-2A, ZNT8	18-31 years (n=576)	>31 (n=556)	≥1 Ab +ve	92% (89 to 94)	93% (91 to 95)	0.4

ESM References

1. Karjalainen J, Knip M, Hyoty H, Leinikki P, Ilonen J, Kaar ML, et al. Relationship between serum insulin autoantibodies, islet cell antibodies and Coxsackie-B4 and mumps virus-specific antibodies at the clinical manifestation of type 1 (insulin-dependent) diabetes. *Diabetologia*. 1988;31(3):146-52.
2. Caillat-Zucman S, Garchon HJ, Timsit J, Assan R, Boitard C, Djilali-Saiah I, et al. Age-dependent HLA genetic heterogeneity of type 1 insulin-dependent diabetes mellitus. *J Clin Invest*. 1992;90(6):2242-50.
3. Vandewalle CL, Decraene T, Schuit FC, De Leeuw IH, Pipeleers DG, Gorus FK. Insulin autoantibodies and high titre islet cell antibodies are preferentially associated with the HLA DQA1*0301-DQB1*0302 haplotype at clinical type 1 (insulin-dependent) diabetes mellitus before age 10 years, but not at onset between age 10 and 40 years. The Belgian Diabetes Registry. *Diabetologia*. 1993;36(11):1155-62.
4. Tait BD, Harrison LC, Drummond BP, Stewart V, Varney MD, Honeyman MC. HLA antigens and age at diagnosis of insulin-dependent diabetes mellitus. *Hum Immunol*. 1995;42(2):116-22.
5. Graham J, Kockum I, Sanjeevi CB, Landin-Olsson M, Nystrom L, Sundkvist G, et al. Negative association between type 1 diabetes and HLA DQB1*0602-DQA1*0102 is attenuated with age at onset. Swedish Childhood Diabetes Study Group. *Eur J Immunogenet*. 1999;26(2-3):117-27.
6. Sabbah E, Savola K, Ebeling T, Kulmala P, Vahasalo P, Ilonen J, et al. Genetic, autoimmune, and clinical characteristics of childhood- and adult-onset type 1 diabetes. *Diabetes Care*. 2000;23(9):1326-32.
7. Petrone A, Galgani A, Spoletni M, Alemanno I, Di Cola S, Bassotti G, et al. Residual insulin secretion at diagnosis of type 1 diabetes is independently associated with both, age of onset and HLA genotype. *Diabetes Metab Res Rev*. 2005;21(3):271-5.
8. Howson JMM, Rosinger S, Smyth DJ, Boehm BO, Todd JA, Grp A-ES. Genetic Analysis of Adult-Onset Autoimmune Diabetes. *Diabetes*. 2011;60(10):2645-53.
9. Thomas NJ, Hill AV, Dayan CM, Oram RA, McDonald TJ, Shields BM, et al. Age of Diagnosis Does Not Alter the Presentation or Progression of Robustly Defined Adult-Onset Type 1 Diabetes. *Diabetes Care*. 2023.
10. Lohmann T, Sessler J, Verlohren HJ, Schroder S, Rotger J, Dahn K, et al. Distinct genetic and immunological features in patients with onset of IDDM before and after age 40. *Diabetes Care*. 1997;20(4):524-9.
11. Vermeulen I, Weets I, Asanghanwa M, Ruige J, Van Gaal L, Mathieu C, et al. Contribution of antibodies against IA-2beta and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. *Diabetes Care*. 2011;34(8):1760-5.
12. Bravis V, Kaur A, Walkey HC, Godsland IF, Misra S, Bingley PJ, et al. Relationship between islet autoantibody status and the clinical characteristics of children and adults with incident type 1 diabetes in a UK cohort. *BMJ Open*. 2018;8(4):e020904.
13. Rogowicz-Frontczak A, Pilacinski S, Wyka K, Wierusz-Wysocka B, Zozulinska-Ziolkiewicz D. Zinc transporter 8 autoantibodies (ZnT8-ab) are associated with higher prevalence of multiple diabetes-related autoantibodies in adults with type 1 diabetes. *Diabetes Res Clin Pract*. 2018;146:313-20.
14. Niechciał E, Rogowicz-Frontczak A, Piłaciński S, Fichna M, Skowrońska B, Fichna P, et al. Autoantibodies against zinc transporter 8 are related to age and metabolic state in patients with newly diagnosed autoimmune diabetes. *Acta Diabetol*. 2018;55(3):287-94.
15. Luo S, Li X, Huang G, Xie Z, Xiang Y, Dai Z, et al. Distinct two different ages associated with clinical profiles of acute onset type 1 diabetes in Chinese patients. *Diabetes Metab Res Rev*. 2020;36(2):e3209.