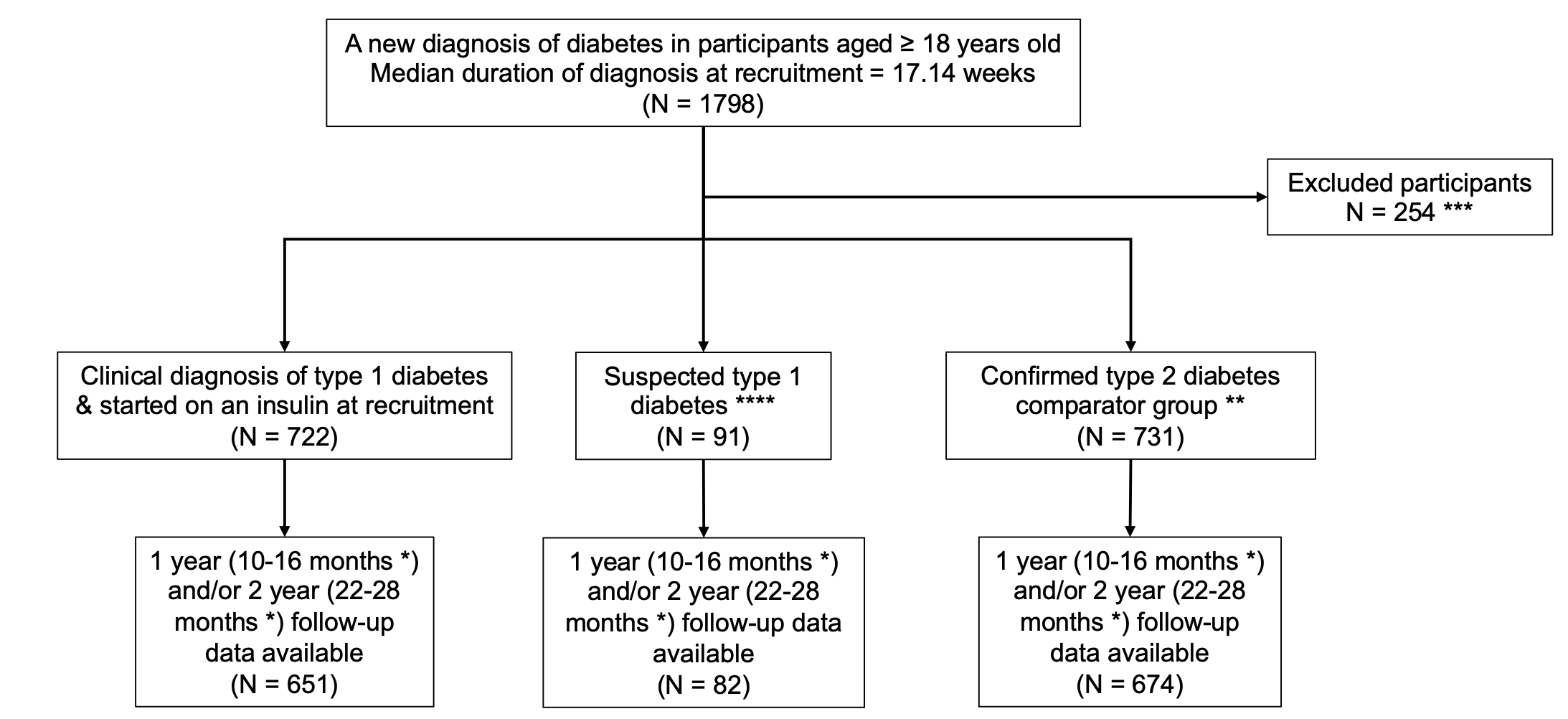
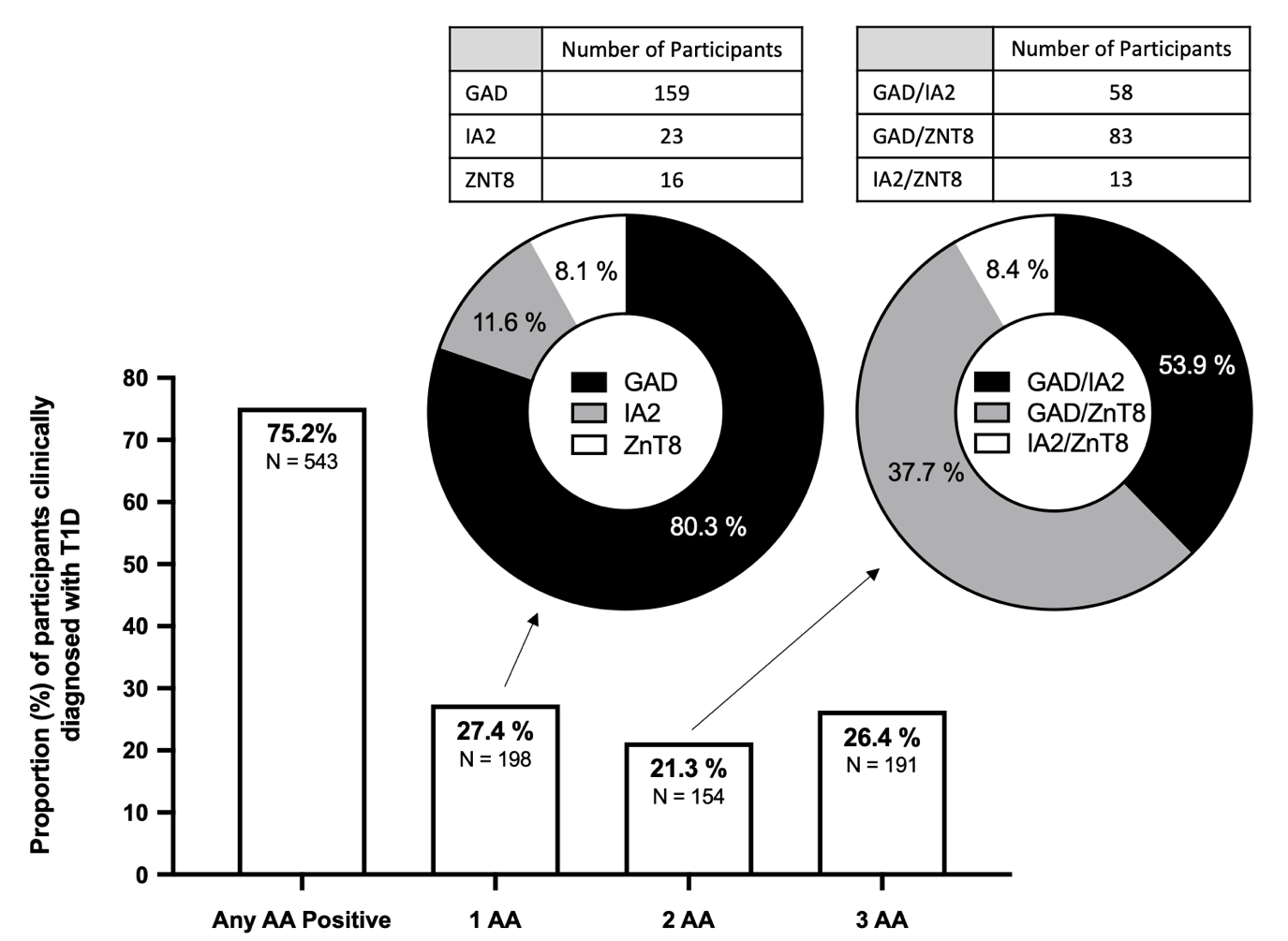
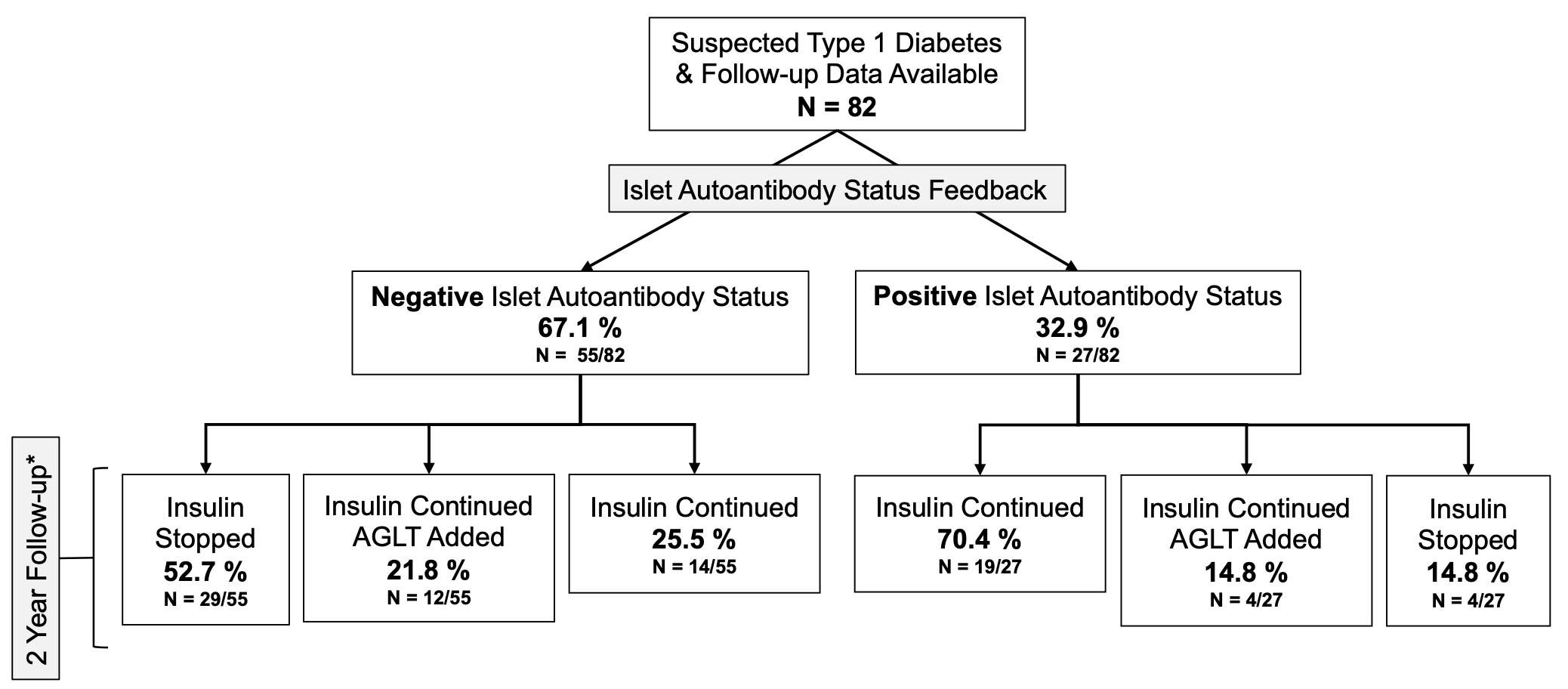
****

**Supplementary Figure 1 - Participant flow diagram.** (\*) These brackets represent the timeframe in which study participants were contacted approximately 1 and/or 2 years after recruitment to record concurrent treatment, hypoglycaemia and health service utilisation. Follow-up data was not available in a total of 137 participants from the three different diagnostic groups. (\*\*) This comparator group had a clinical diagnosis of type 2 diabetes alongside being both islet autoantibody negative and not treated with insulin at recruitment. (\*\*\*) Excluded participants included those not receiving insulin treatment from diagnosis, and did not have a diagnosis of type 1 diabetes (reflecting clinical uncertainty, or other diabetes type) or a clinical diagnosis of type 2 diabetes that were either islet autoantibody positive or receiving insulin at recruitment. (\*\*\*\*) ‘Suspected type 1 diabetes’ represents participants where a clinical diagnosis was uncertain who were receiving insulin at recruitment.



**Supplementary Figure 2 - Islet autoantibody (AA) frequency of participants with type 1 diabetes (T1D) who met the study criteria.** The distribution and number (N) of participants with islet autoantibodies (GAD, IA2 & ZNT8) as a proportion of the type 1 diabetes cohort meeting the study criteria and the detailed distribution of participants for those with 1 or 2 islet autoantibodies.

****

**Supplementary Figure 3 - Feeding back islet autoantibody status can motivate insulin treatment alteration when a clinical diagnosis is uncertain but type 1 diabetes is suspected with insulin being received at recruitment**. The participants included in this analysis were receiving insulin at recruitment and had at least one completed follow-up visit. Islet autoantibody positive and negative participants were separated & treatment alterations associated with insulin were identified. AGLT - adjuvant glucose lowering therapy; including either/or a: metformin, sulphonylurea, DPP4 inhibitor, SGLT-2 inhibitor, glitazone or GLP-1 receptor agonist.



**Supplementary Figure 4 - Mean HbA1c at study recruitment and latest follow up in participants who had a clinically uncertain diagnosis and had been receiving insulin, by antibody status and treatment change.** Error bars represent 95% confidence intervals. Recruitment HbA1c was assessed at a median 4 months diabetes duration. Last recorded HbA1c was assessed at a median 24 months later (median diabetes duration 28.5 months). The data represented is of islet autoantibody positive (N=27/82) and negative (N=55/82) participants who had follow up data available for both treatment and a HbA1c > 3 months after any alteration. Combined Treatments – the collective available data irrespective of any treatment continuation or alteration, Insulin continued – participants whose Insulin was continued (N=14/55), Insulin stopped – participants whose Insulin was stopped (N=29/55), Insulin + AGLT added – participants whose Insulin continued alongside the addition of an adjuvant glucose lowering therapy (N=12/55), which included either/or a: metformin, sulphonylurea, DPP4 inhibitor, SGLT-2 inhibitor, glitazone or GLP-1 receptor agonist.



**Supplementary Figure 5 - Islet autoantibody reporting form for both participant and treating clinician if autoantibody negative.**



**Supplementary Figure 6 - Islet autoantibody reporting form for both participant and treating clinician if autoantibody positive**

|  |  |  |
| --- | --- | --- |
|  | Type 1 Diabetes (N = 179) mean (95% CI) or % (95% CI) | Type 2 Diabetes (N = 731) mean (95% CI) or % (95% CI) |
| **Clinical Features** |  |  |
| **Male (%)** | 72.9 (66.3-79.5) | 57.6 (54.0-61.2) |
| **Ethnicity (% White European)** | 86.0 (80.9-91.2) | 85.2 (82.6-87.8) |
| **Age at diagnosis (years)** | 42.7 (40.6-44.8) | 50.4 (49.5-51.3) |
| **Duration of diabetes at recruitment (weeks)** | 17 (15-19) | 24 (23-25) |
| **BMI at recruitment** | 27.4 (26.6-28.2) | 33.3 (32.8-33.9) |
| **DKA at diagnosis (% Yes)** | 20.7 (14.7-26.7) | 0.5 (0.01-1.1) |
| **Osmotic symptoms at diagnosis (% Yes)** | 91.1 (86.8-95.3) | 62.6 (59.1-66.1) |
| **Weight loss pre-diagnosis (% Yes)** | 76.0 (69.7-82.3) | 16.8 (14.1-19.6) |
| **Other auto-immune condition (% Yes)** | 3.9 (1.1-6.8) | 8.5 (6.5-10.5) |
| **Biochemical/Genetic Features** |  |  |
| **HbA1c at diagnosis (mmol/mol)** | 109.8 (106.1-113.6) | 69.9 (68.2-71.4) |
| **Glucose at diagnosis (mmol/L)** | 23.6 (21.8-25.4) | 12.6 (11.8-13.4) |
| **Plasma C-Peptide at recruitment \* (pmol/L)** | 607.6 (500.5-737.5) | 1792.3 (1710.9-1877.6) |
| **UCPCR at recruitment \* (nmol/mmol)** | 1.09 (0.85-1.39) | 2.66 (2.47-2.87) |
| **T1D-GRS** | 10.85 (10.43-11.27) | 10.12 (9.93-10.32) |

**Supplementary Table 1 - Clinical characteristics of participants with negative islet autoantibodies and clinically diagnosed type 1 diabetes and type 2 diabetes.** The T1D-GRS results for participants with type 1 diabetes (N=154/179) & type 2 diabetes (N=623/731) includes only those who were of White European decent with appropriate genetic data available. (\*) The results presented for the plasma C-peptide and UCPCR is the geometric mean with all relevant statistics performed on the log transformed values. T1D-GRS, Type 1 Diabetes Genetic Risk Score; UCPCR, Urinary C-Peptide Creatinine Ratio; DKA, Diabetic Ketoacidosis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Insulin Continued (N = 104) mean (95% CI) or % (95% CI) | Insulin Stopped (N = 37) mean (95% CI) or % (95% CI) | *P* value |
| **Clinical Features** |  |  |  |
| **Male (%)** | 75.5 (67.0-84.0) | 70.3 (54.8-85.7) | 0.54 |
| **Ethnicity (% White European)** | 84.6 (77.6-91.7) | 89.2 (78.7-99.7) | 0.50 |
| **Age at diagnosis (years)** | 42.4 (39.7-45.2) | 42.2 (37.8-46.5) | 0.92 |
| **Duration of diabetes at recruitment (weeks)** | 18 (15-21) | 13 (9-17) | 0.05 |
| **BMI at recruitment** | 25.7 (24.8-26.6) | 30.5 (28.3-32.7) | <0.001 |
| **DKA at diagnosis (% Yes)** | 25.0 (16.5-33.5) | 16.2 (3.8-28.7) | 0.27 |
| **Osmotic symptoms at diagnosis (% Yes)** | 92.3 (87.1-97.5) | 83.8 (71.3-96.2) | 0.14 |
| **Weight loss pre-diagnosis (% Yes)** | 79.8 (72.0-87.7) | 59.5 (42.9-76.1) | 0.02 |
| **Other auto-immune condition (% Yes)** | 3.8 (0.1-7.6) | 2.8 (0.1-8.4) | 0.77 |
| **Biochemical/Genetic Features** |  |  |  |
| **HbA1c at diagnosis (mmol/mol)** | 112.5 (107.4-117.7) | 102.5 (95.4-109.6) | 0.04 |
| **Glucose at diagnosis (mmol/L)** | 23.7 (21.4-26.1) | 21.4 (17.4-25.5) | 0.33 |
| **Plasma C-Peptide at recruitment \* (pmol/L)** | 430.7 (324.6-571.5) | 1233.1 (983.3-1546.2) | <0.001 |
| **UCPCR at recruitment \* (nmol/mmol)** | 1.05 (0.75-1.47) | 1.66 (1.13-2.45) | 0.13 |
| **T1D-GRS** | 11.53 (11.02-12.04) | 9.47 (8.52-10.42) | <0.001 |

**Supplementary Table 2 – Clinical characteristics of islet autoantibody negative participants clinically diagnosed with type 1 diabetes in the cohort who met the study criteria and had at least one completed follow-up visit, defined by insulin treatment.** The T1D-GRS for participants whose insulin was continued (N=90/104) or stopped (N=33/37) includes only those who were of White European decent with appropriate genetic data available. *P* values given for continuous variables are 2 sample t-tests and Pearson Chi-squared for categorical variables. (\*) The results presented for the plasma C-peptide and UCPCR is the geometric mean with the statistics performed on the log transformed values. T1D-GRS, Type 1 Diabetes Genetic Risk Score; UCPCR, Urinary C-Peptide Creatinine Ratio; DKA, Diabetic Ketoacidosis.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | SR0032 | SR1047 | SR1064 | SR2646 | SR3066 |
| **Clinical Features** |  |  |  |  |  |
| **Gender** | Female | Male | Male | Male | Female |
| **White European Ethnicity** | Yes | Yes | No | Yes | Yes |
| **Age at diagnosis (years)** | 28 | 32 | 40 | 25 | 62 |
| **Duration of diabetes at recruitment (weeks)** | 2 | 3 | 8 | 5 | 1 |
| **BMI at recruitment** | 22.1 | 27.2 | 30.1 | 21.8 | 27.7 |
| **DKA at diagnosis** | No | No | No | Yes | No |
| **Osmotic symptoms at diagnosis** | Yes | Yes | Yes | Yes | Yes |
| **Weight loss pre-diagnosis** | Yes | Yes | Yes | Yes | Yes |
| **Other auto-immune condition** | No | No | No | No | Yes (Hypothyroidism) |
| **Biochemical/Genetic Features** |  |  |  |  |  |
| **HbA1c at diagnosis (mmol/mol)** | 75 | 137 | 105 | 83 | 144 |
| **Glucose at diagnosis (mmol/L)** | Unavailable | Unavailable | 25.5 | Unavailable | 25.9 |
| **Plasma C-Peptide at recruitment (pmol/L)** | 699 | 1220 | 1680 | 165 | 744 |
| **UCPCR at recruitment (nmol/mmol)** | Unavailable | 2.49 | 1.03 | 0.14 | 2.93 |
| **T1D-GRS** | 13.35 | 11.41 | 9.44 | 14.66 | 9.14 |
| **Number of Islet autoantibodies** | 3 | 2 | 1 | 3 | 1 |
| **Type of Islet autoantibodies** | GAD65, IA2, ZNT8 | IA2, ZNT8 | GAD65 | GAD65, IA2, ZNT8 | ZNT8 |

**Supplementary Table 3 – Individual characteristics of islet autoantibody positive participants with clinically diagnosed type 1 diabetes stopping insulin within the 2 year follow up period.** T1D-GRS, Type 1 Diabetes Genetic Risk Score; UCPCR, Urinary C-Peptide Creatinine Ratio; DKA, Diabetic Ketoacidosis.

|  |  |  |  |
| --- | --- | --- | --- |
|  | Islet Autoantibody Positive (N = 29) mean (95% CI) or % (95% CI) | Islet Autoantibody Negative (N = 62) mean (95% CI) or % (95% CI) | *P* value |
| **Clinical Features** |  |  |  |
| **Male (%)** | 58.6 (39.6-77.7) | 67.8 (55.5-80.1) | 0.40 |
| **Ethnicity (% White European)** | 86.2 (72.9-99.6) | 71.0 (59.3-82.6) | 0.11 |
| **Age at diagnosis (years)** | 45.0 (39.8-50.3) | 46.5 (43.4-49.6) | 0.61 |
| **Duration of diabetes at recruitment (weeks)** | 15 (9-21) | 16 (12-19) | 0.86 |
| **BMI at recruitment** | 28.6 (26.1-31.1) | 29.6 (27.9-31.3) | 0.47 |
| **DKA at diagnosis (% Yes)** | 3.4 (-3.6-10.5) | 8.1 (1.1-15.0) | 0.41 |
| **Osmotic symptoms at diagnosis (% Yes)** | 100 | 93.5 (87.3-99.8) | 0.16 |
| **Weight loss pre-diagnosis (% Yes)** | 75.9 (59.3-92.4) | 67.7 (55.8-79.7) | 0.43 |
| **Other auto-immune condition (% Yes)** | 17.9 (2.7-33.0) | 3.3 (-1.3-7.9) | 0.02 |
| **Biochemical/Genetic Features** |  |  |  |
| **HbA1c at diagnosis (mmol/mol)** | 103.4 (92.9-113.9) | 113.1 (106.9-119.3) | 0.09 |
| **Glucose at diagnosis (mmol/L)** | 19.4 (15.6-23.2) | 24.1 (20.2-28.0) | 0.16 |
| **Plasma C-Peptide at recruitment \* (pmol/L)** | 747.8 (550.9-1015.2) | 1159.4 (967.0-1390.2) | 0.01 |
| **UCPCR at recruitment \* (nmol/mmol)** | 1.88 (1.18-3.00) | 2.23 (1.82-2.74) | 0.43 |
| **T1D-GRS** | 12.60 (11.17-11.44) | 9.98 (9.22-10.74) | <0.001 |

**Supplementary Table 4 - Clinical characteristics of participants in the cohort who had a clinically uncertain diagnosis and had been receiving insulin who met the study criteria, defined by islet autoantibody status,** **as either negative (no autoantibodies) or positive (≥1 autoantibodies**)**.** The T1D-GRS result for autoantibody positive (N=44/62) & negative (N=27/29) participants include only those who were of White European decent with appropriate genetic data available. *P* values given for continuous variables are 2 sample t-tests and Pearson Chi-squared for categorical variables. (\*) The results presented for the plasma C-peptide and UCPCR is the geometric mean with the statistics performed on the log transformed values. T1D-GRS, Type 1 Diabetes Genetic Risk Score; UCPCR, Urinary C-Peptide Creatinine Ratio; DKA, Diabetic Ketoacidosis