General population screening for T1D: Experience from Sweden

Daniel Agardh, PhD, MD
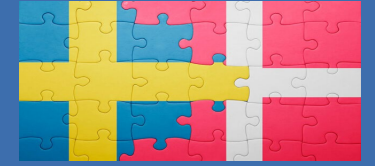
Celiac Disease and Diabetes Unit, Lund University, Malmö, Sweden

DiaUnion est. 2020

DiaUnion is a collaboration between **Lund University** and **Steno Diabetes Center Copenhagen**

DiaUnion started in 2020 with the aim to create a screening program in Sweden and Denmark for type 1 diabetes and related autoimmune diseases

DiaUnion's first focus is to build an infrastructure for early detection of type 1 diabetes, celiac disease and autoimmune thyroid disease in the Öresund Region

Why the TRIAD?

- Type 1 Diabetes (T1D), Celiac Disease (CD), Autoimmune Thyroid Disease (AITD)

- Common chronic diseases affecting children and adolescents (0.5–3%)

- Frequently co-occurs in families

- No cure – lifelong treatment (insulin, gluten-free diet, levothyroxin)

- Clinical onset is preceded by the presence of disease-specific autoantibodies

Different screening approaches

Screening of children randomly invited from the general pediatric population in the Skåne County, Sweden

Screening of siblings (i.e., FDRs) of patients with T1D in Copenhagen, Denmark

FDR, first degree relatives.

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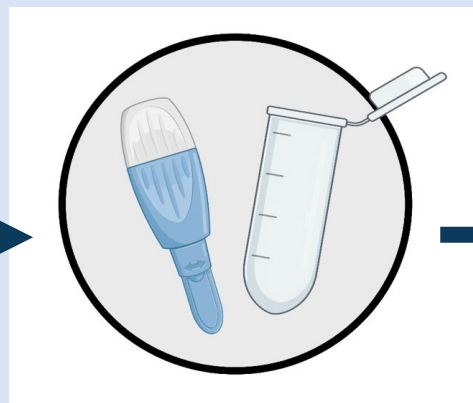
Screening of Swedish children

Step 1. Invitation	Step 2. Sampling	Step 3. Testing	Step 4. Follow-up

Skåne County, Sweden (n=1.4 million)
- Two age groups:
  - 6–9 years
  - 13–16 years
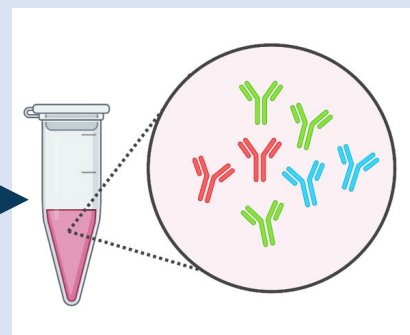- General population (n=68,000)
- Invitation to screening (n=20,000)

Home capillary sampling kit
- Kit sent to home address
- Finger prick (>250 uL)
- Samples sent back to the lab by regular mail

Detection of eight autoantibodies:
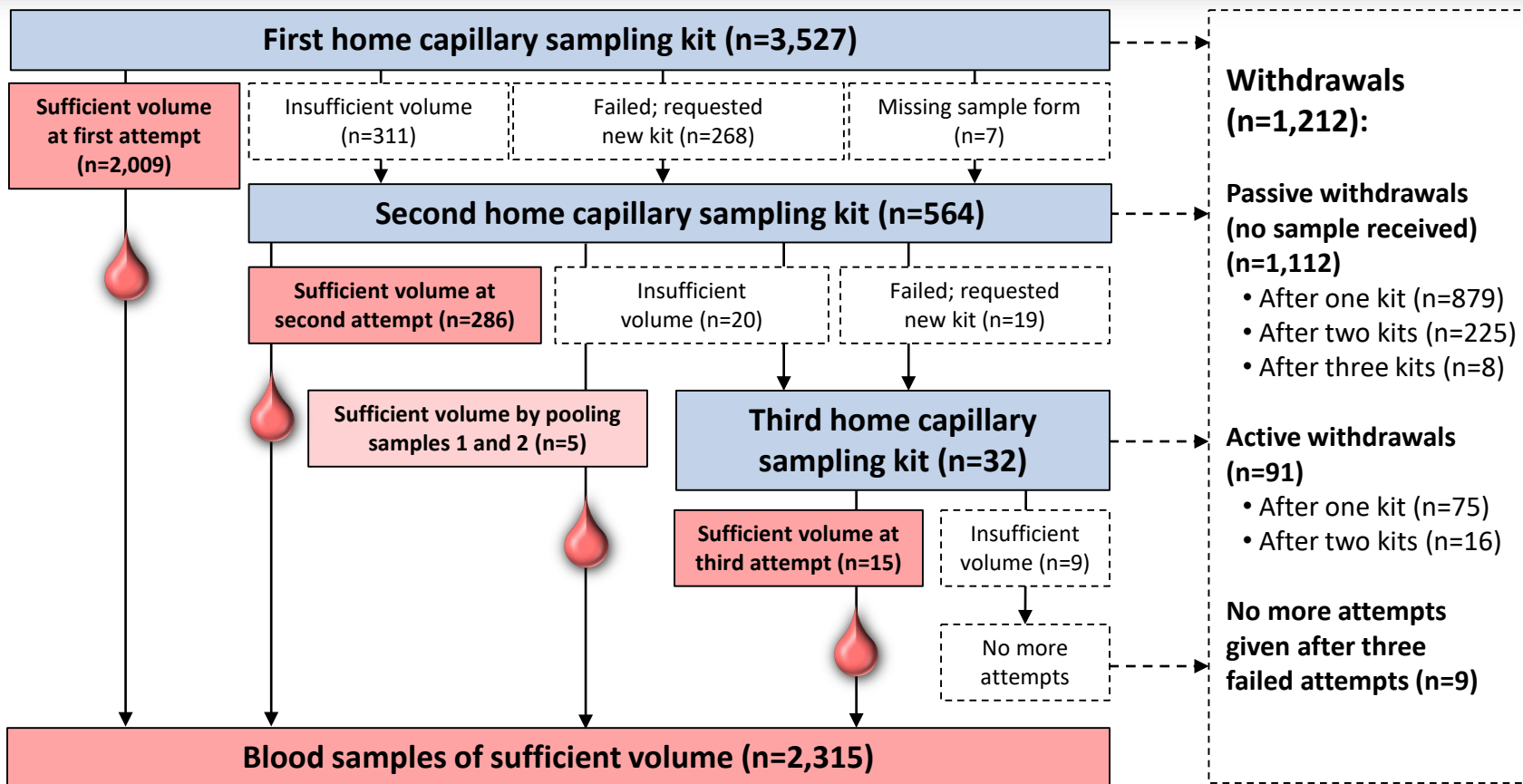- T1D (IAA, GADA, IA-2A, ZnT8A)
- CD (IgA-tTG, IgG-tTG)
- AITD (TPOA, THGA)
- 1. Radiobinding assays (RBA); chemiluminescent immunoassay
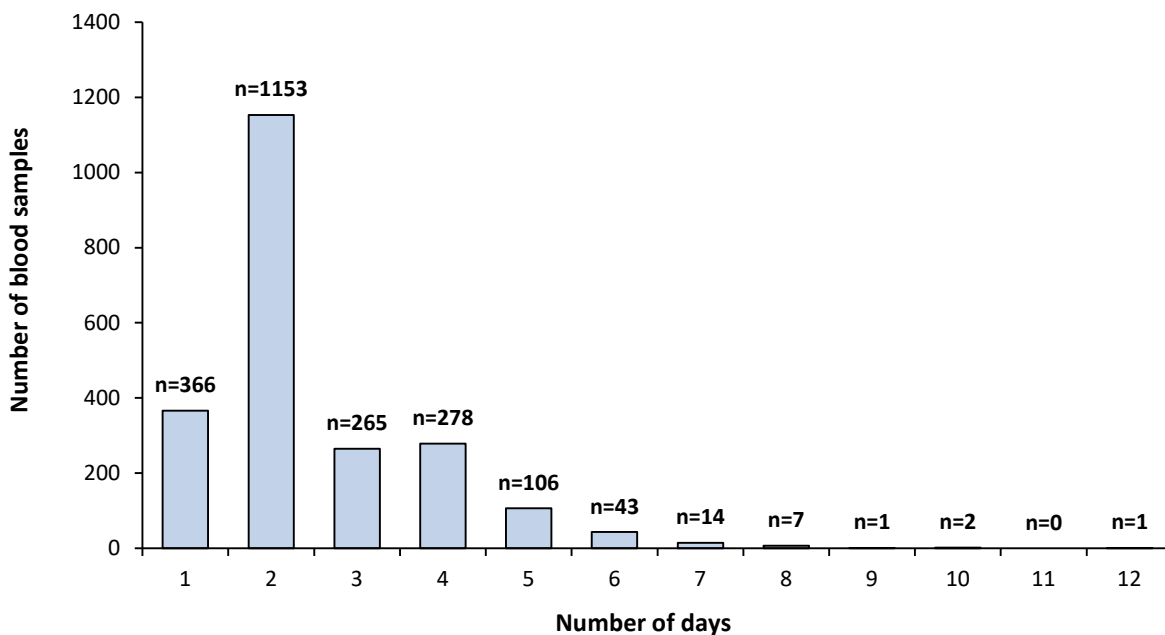- 2. Antibody-detection by agglutination-PCR (ADAP)

(Aab+) children:
- A second sample median 3.8 (range 1.9–15) mo
- Persistent Aab+ children referred to pediatrician for clinical follow-up

ADAP, agglutination-PCR; GADA, glutamic acid decarboxylase antibodies; IAA, insulin autoantibodies; IA-2A, IA-2 autoantigen; IgA, immunoglobulin A; IgG, immunoglobulin G; THGA, thyroglobulin autoantibodies; TPOA, thyroperoxidase autoantibodies; tTG, tissue transglutaminase; ZnT8A, zinc transporter 8 autoantibody. **Communication provided by speaker.** The DiaUnion TRIAD study is a collaboration between Lund University, Steno Diabetes Center Copenhagen and Medicon Valley Alliance, for early detection of T1D and two genetically related autoimmune diseases (CD and AITD). For more information on the DiaUnion TRIAD study, including the predicted end date, see: https://portal.research.lu.se/en/projects/screening-for-Type-1-diabetes-celiac-disease-and-thyroiditis-in-c [Last accessed October 2023]

Feasibility of home sampling

First home capillary sampling kit (n=3,527)

Sufficient volume at first attempt (n=2,009)

Insufficient volume (n=311) — Failed; requested new kit (n=268) — Missing sample form (n=7)

Second home capillary sampling kit (n=564)

Sufficient volume at second attempt (n=286)

Insufficient volume (n=20) — Failed; requested new kit (n=19)

Sufficient volume by pooling samples 1 and 2 (n=5)

Third home capillary sampling kit (n=32)

Sufficient volume at third attempt (n=15)

Insufficient volume (n=9) — No more attempts

Blood samples of sufficient volume (n=2,315)

Withdrawals (n=1,212):

Passive withdrawals (no sample received) (n=1,112)
- After one kit (n=879)
- After two kits (n=225)
- After three kits (n=8)

Active withdrawals (n=91)
- After one kit (n=75)
- After two kits (n=16)

No more attempts given after three failed attempts (n=9)

- **3,527** consents **(18.0%)**
- **4,123** kits sent out
- **2,315** blood samples of sufficient volume **(65.6%)**
- **1,112** no sample **(31.5%)**
- **91** active withdrawals
  - **58** due to concerns about blood draw **(63.7%)**

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Quality of samples

Days between sample draw date and sample process date (registered in 2,236 samples)

Median: 2 days

HEMOLYSIS? (registered in 2,301 samples)
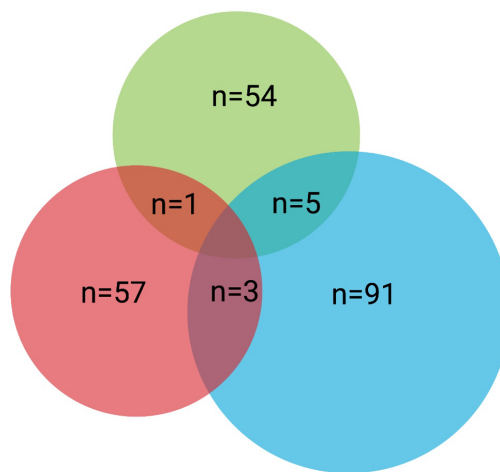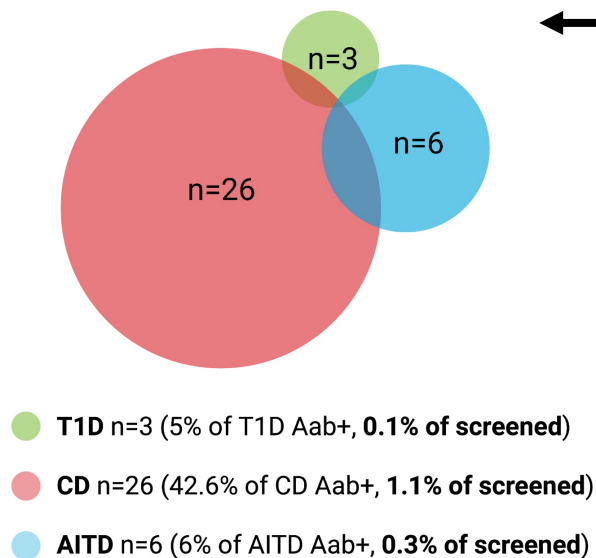
No hemolysis
n=1,471 (63.6%)

Moderate hemolysis
n=620 (26.9%)

Gross hemolysis
n=210 (9.1%)

Results of screening (n=2271)

AAb+ in screening
n=211 (9.3%)

Diagnosed after screening
n=35 (1.5%)

n=54

n=3

n=1   n=5

n=6

n=26

n=57   n=3   n=91

Positive autoantibodies
Normal clinical investigation
"At risk individuals"
n=176

Recruited to clinical intervention
study (PAL)
n=65

- **T1D** n=3 (5% of T1D Aab+, **0.1% of screened**)
- **CD** n=26 (42.6% of CD Aab+, **1.1% of screened**)
- **AITD** n=6 (6% of AITD Aab+, **0.3% of screened**)

- **T1D Aab+** n=60 (**2.6% of screened**)
- **CD Aab+** n=61, (**2.7% of screened**)
- **AITD Aab+** n=99, (**4.4% of screened**)
- **Aab+ for multiple TRIAD diseases** n=9 (**0.4% of screened**)

PAL
Prevention av Autoimmunitet med Laktobaciller

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Islet Aab+ (n=60)

46 — **T1D Single Aab+, n=46**
(76.7% of T1D Aab+, 2.0% of screened)

11 — **T1D Multiple Aab+, n=14**
(23.3% of T1D Aab+, 0.6 % of screened)

3 — **T1D Diagnosis Aab+, n=3**
(5.0% of T1D Aab+, 0.1% of screened)

	No. (%)
All screened	**2,271 (100)**
Islet Aab+	**60 (2.6)**
IAA	30 (1.3)
GADA	37 (1.6)
IA-2A	10 (0.4)
ZnT8A	9 (0.4)

Clinical follow-up

Screening sample islet Aab+

↓

Confirmatory sample +
HbA1c

Aab–
+
Normal HbA1c

Aab+
+
Normal HbA1c

Aab+
+
Abnormal HbA1c

Information from pediatrician

Information from pediatrician about risk
+
Information about intervention study, if eligible

Information from pediatrician

No follow-up

Multiple Aab+
HbA1c every 3 months for 1 year
Information from pediatrician

Single Aab+
HbA1c after 1 year
Information from pediatrician

Referral to pediatric clinic; OGTT

TRIAD among family members

Diagnosis in FDR to Aab+ children (n=211)

TRIAD among family members
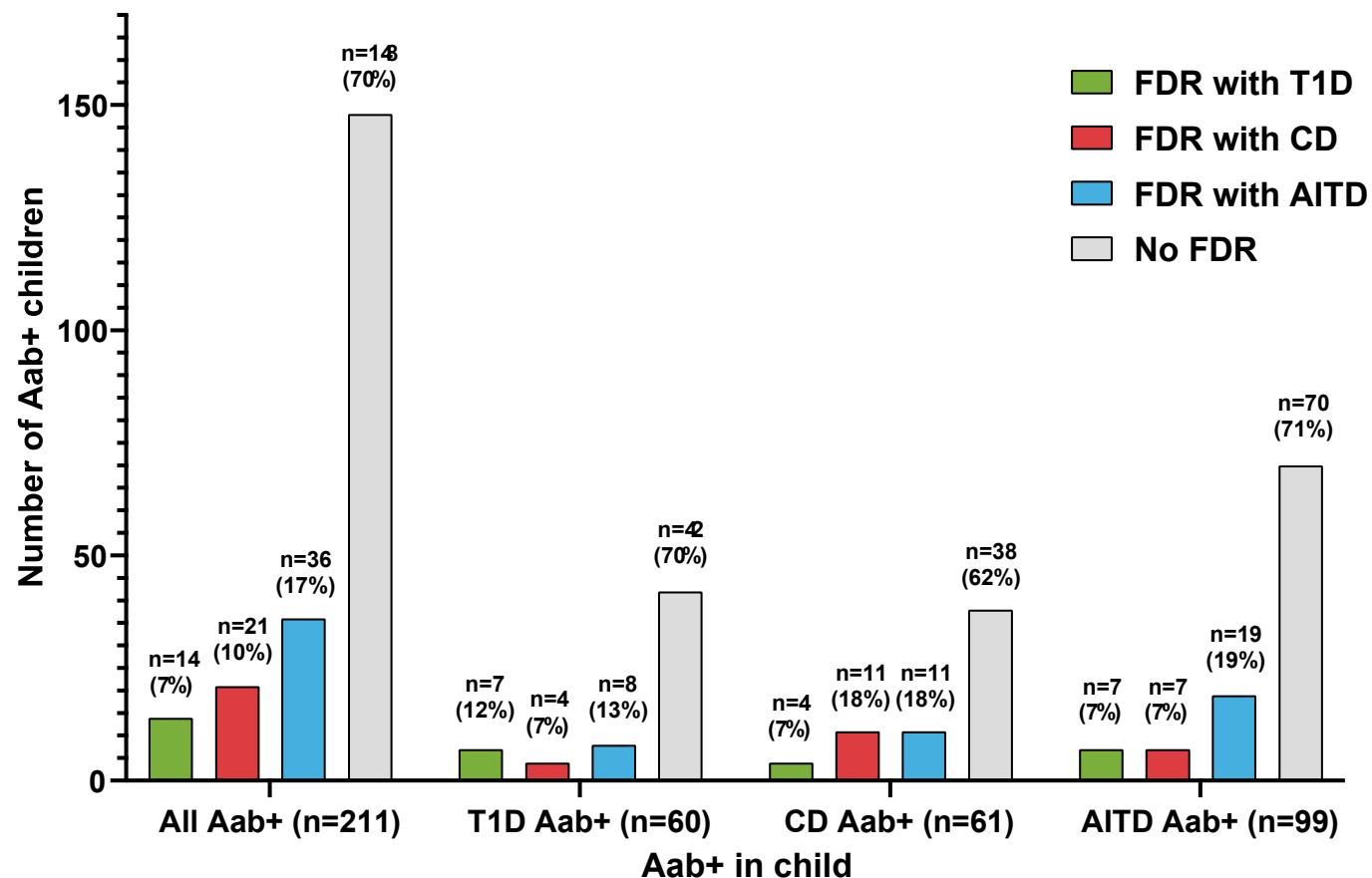
30% of Aab+ children had an FDR with a TRIAD-disease
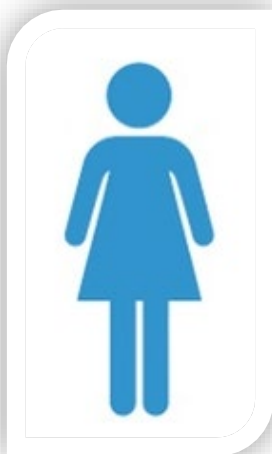
>2/3 were mothers
AITD was the most common disease in mothers (70%)
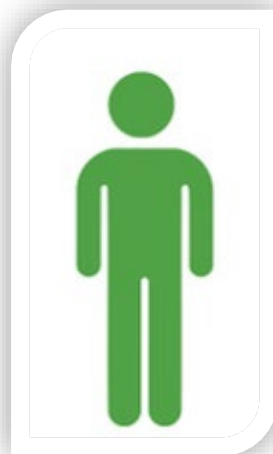
>1/6 were fathers
T1D was the most common disease in fathers (50%)
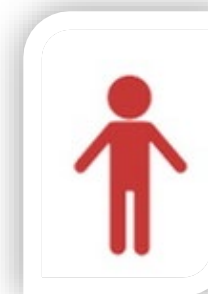
<1/6 were siblings
CD was the most common disease in siblings (63%)

In 52% the FDR had another disease than the child was screened positive for

1. Biobank samples (no follow up; n=1,420)
2. ADAP used as the screening assay
3. RBA used to confirm Aab+

Aab+ results confirmed by RBA showed:
Any TRIAD autoantibody:
- 13.5% Danish T1D FDRs
- 5.6% of Swedish pediatric GP

Any T1D autoantibody:
- 7.5% of Danish T1D FDRs
- 1.1% of Swedish pediatric GP

Multiple T1D autoantibodies:
- 4.6% of Danish T1D FDR
- 0.6% of Swedish pediatric GP

Aab+	Danish T1D FDRs N=192/1,420 (13.5%) n/N (%)	Swedish children N=127/2,271 (5.6%) n/N (%)
GADA	89/1,420 (6.3%)	22/2,272 (1.0%)
IAA	43/1,420 (3.0%)	8/2,272 (0.4%)
IA-2A	38/1,420 (2.7%)	8/2,272 (0.4%)
ZnT8	28/1,420 (2.0%)	3/2,271 (0.1%)
TPOA	55/1,420 (3.9%)	52/2,272 (2.3%)
tTGA	55/1,420 (3.9%)	55/2,272 (2.4%)

DiaUnion 1.5 (2022–2023):

1. Swedish general pediatric population:

- 1. ADAP screening assay
- 2. RBA confirmation assay
- 13,498 children ages 6–9 years and 13–16 years invited
- So far 2407 children enrolled, 17.8% consent rate (**Fig.1**)
- So far 1553 samples collected, 11.5% participating rate (**Fig.2**)
- 31 (2.0%) reported a TRIAD disease (1.0% CD, 0.2% T1D, 0.1% AITD)
- 333 (21.4%) children reported to have a FDRs with TRIAD disease
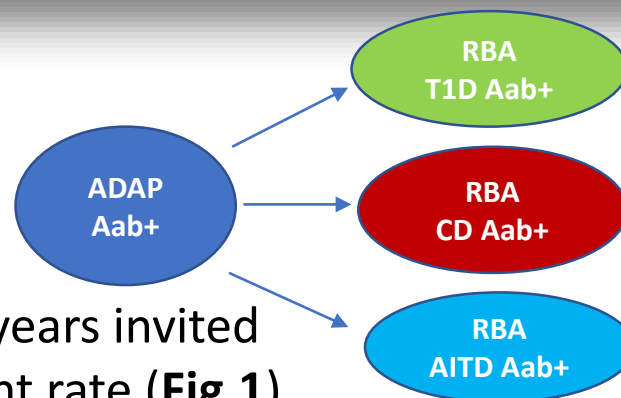
2. Danish T1D-FDRs (siblings, children, parents):

- Age <40 years, 1,500 invited to screening
- ADAP screening assay
- RBA confirmation assay
- Analysis pending

ADAP Aab+ → RBA T1D Aab+

ADAP Aab+ → RBA CD Aab+

ADAP Aab+ → RBA AITD Aab+

Fig. 1. Consent rate

Fig. 2. Sample rate

ADAP vs RBA for GADA
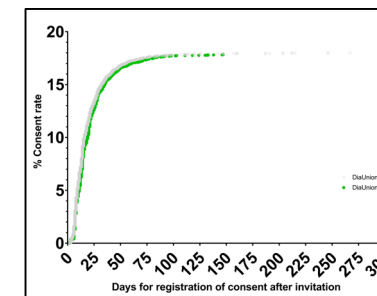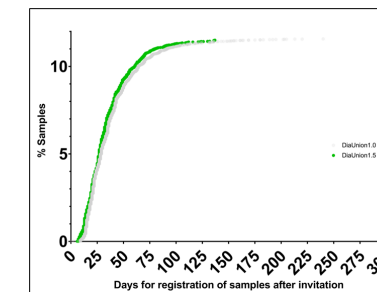
DiaUnion 1.0 (2021-2022)

- 2273 samples analysed in both ADAP and RBA
- The concordance agreement, Cohen's kappa κ coefficient, between the assays were 0.542
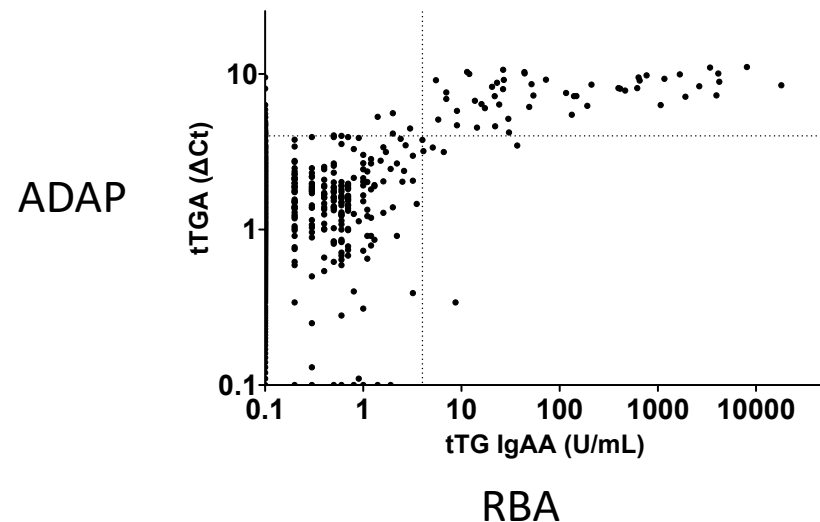- Prevalence of confirmed GADA 1.0%
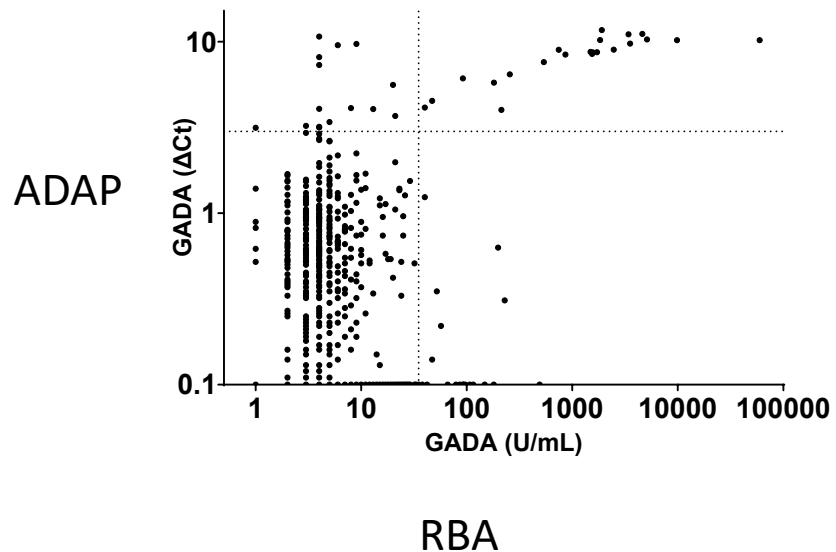
DiaUnion 1.5 (2023)

- ADAP first-line screening (cut-off 98th percentile)
- RBA confirmation assay
- 44/957 (4.6%) above cut-off in ADAP
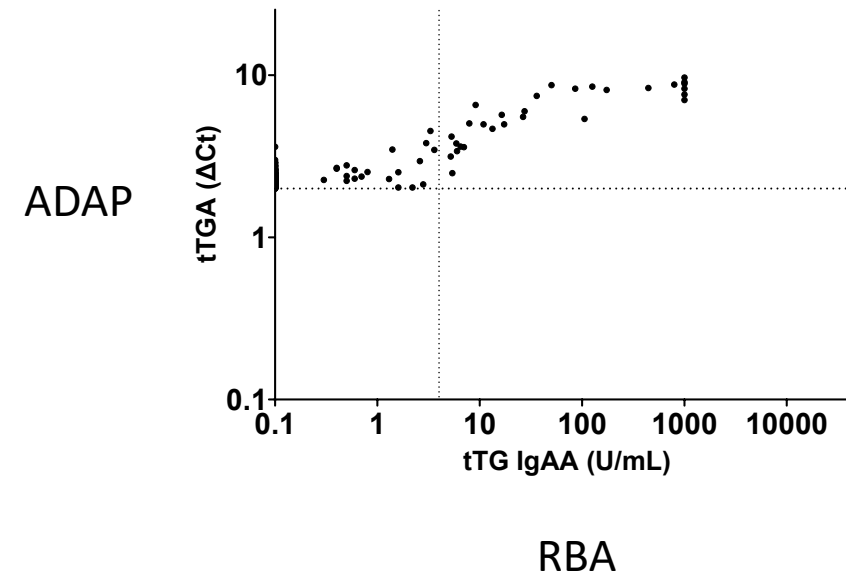- 13/44 (29.5%) confirmed GADA positive in RBA
- Prevalence of confirmed GADA 1.4%
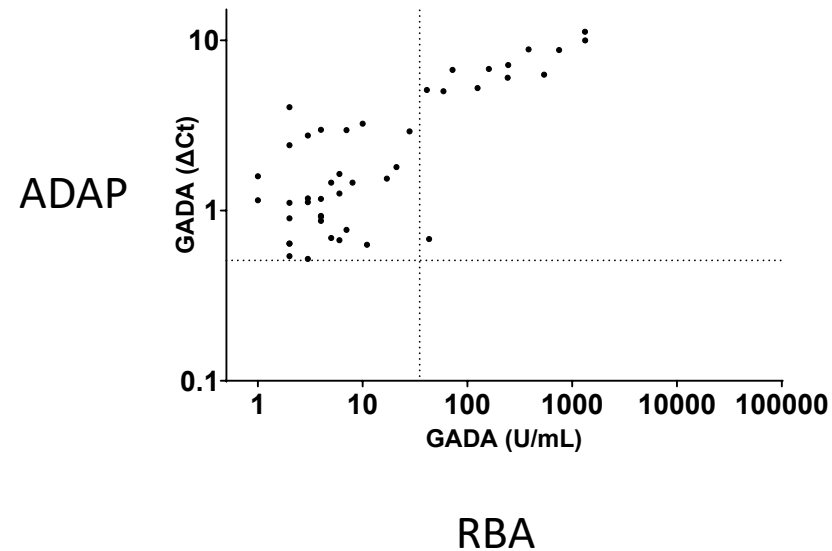
ADAP

RBA

ADAP

RBA

ADAP vs RBA for tTGA

DiaUnion 1.0 (2021-2022)

- 2273 samples analysed in both ADAP & RBA
- The concordance agreement, Cohen's kappa κ coefficient, between the assays were 0.698 (IgA) and 0.675 (IgG)
- Prevalence of confirmed tTGA 2.4%
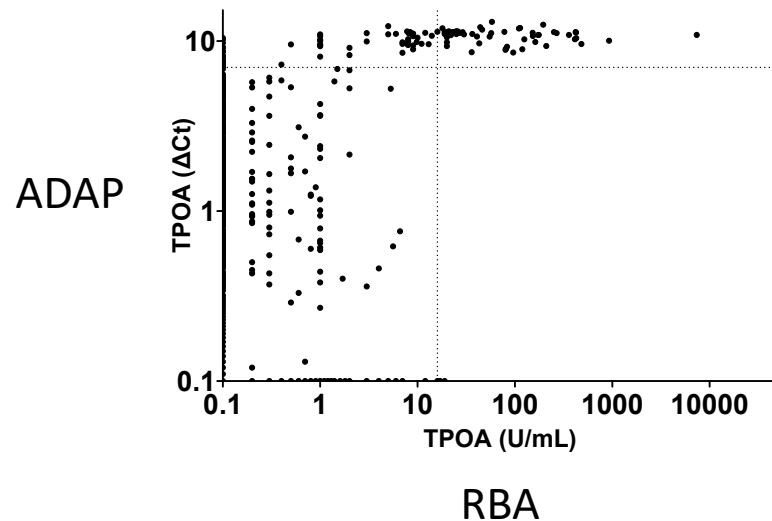

DiaUnion 1.5 (2023)

- ADAP first-line screening (cut-off 75th percentile)
- RBA confirmation assay
- 222/957 (23.2%) above cut-off in ADAP
- 33/222 (14.9%) confirmed tTGA (IgA+IgG) positive in RBA
- Prevalence of confirmed tTGA 3.4%

ADAP vs RBA for TPOA

DiaUnion 1.0 (2021-2022)

- 2273 samples analysed in both ADAP & RBA
- The concordance agreement, Cohen's kappa κ coefficient, between the assays were 0.595
- Prevalence of confirmed TPOA 2.3%

DiaUnion 1.5 (2023)

- ADAP first-line screening (cutoff 90th percentile)
- RBA confirmation assay
- 44/957 (4.6%) above cut-off in ADAP
- 27/44 (61.4%) confirmed positive in RBA
- Prevalence of confirmed TPOA 2.8%

Summary
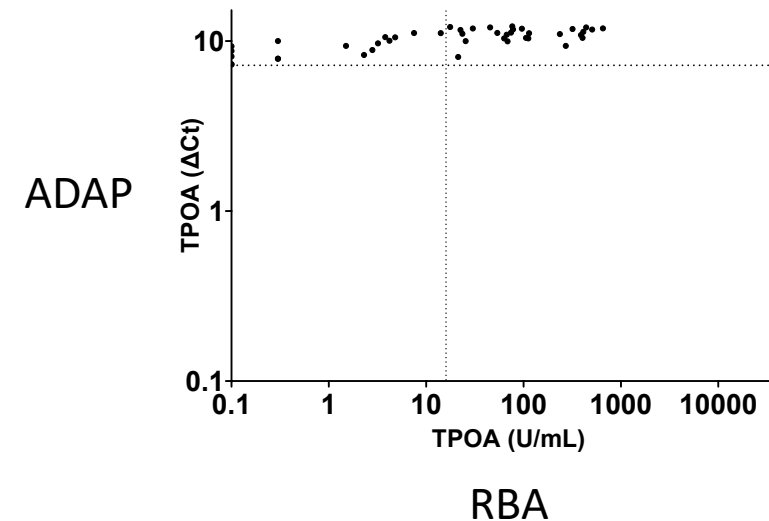
- DiaUnion boosts screening for T1D by including CD and AITD

- DiaUnon´s 1st screening of the Swedish GP population found islet autoimmunity in 2.6%, multiple islet autoantibodies in 0.6%, and T1D in 0.1%

- Results DiaUnon´s 2nd screening of the Swedish GP population pending, but confirms consent rate (18%) and successful participation rate (12%).

- Home sampling is feasible, but can be optimized by collecting smaller sample volumes for multiplex assays

- The multiplex ADAP assay is promising as a screening method, but further evaluation is needed before considering it as first-line screening for the GP

- DiaUnion´s next goal is to scale up screening to 30,000 Swedish children from the GP and 15,000 Danish T1D FDRs

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