Diabetologia (2026) 69:1282–1294
https://doi.org/10.1007/s00125-026-06680-y

ARTICLE

Feasibility and performance of minimal-volume capillary blood screening for type 1 diabetes and coeliac disease autoantibodies across all age groups: the UNISCREEN population study

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Received: 30 May 2025 / Accepted: 15 December 2025 / Published online: 10 February 2026
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Abstract

Aims/hypothesis The UNISCREEN study investigated the feasibility of minimally invasive capillary blood sampling combined with novel antibody tests for population-wide screening of type 1 diabetes and coeliac disease autoantibodies across all age groups, with secondary objectives to evaluate the prevalence and age-related distribution of these autoantibodies in a general Northern Italian population.

Methods Between April and October 2023, we screened 1532 residents (50.1% of eligible population) of Cantalupo, Milan, aged 1–100 years. Capillary blood samples were collected by fingerprick from all participants. A subset of 20 autoantibody-positive individuals provided confirmatory venous samples. Islet autoantibody screening employed a novel solid-phase capture luciferase immunoprecipitation system (LIPS) 3-screen assay requiring only 1 µl of serum for simultaneous detection of GADA, IA-2A and ZnT8A, plus a separate IAA assay. Positive samples underwent confirmatory testing with individual LIPS assays using truncated GADA to improve specificity. Coeliac disease screening used a tissue transglutaminase IgA (TGA-IgA) LIPS assay. Capillary–venous sample concordance and assay format comparisons validated the methodology.

Results Among 1454 individuals without known diabetes, islet autoantibody prevalence was 2.3% (95% CI 1.6, 3.2), with 70.6% having single autoantibodies and 29.4% having multiple autoantibodies. Among 73 individuals with type 2 diabetes, 9.6% (95% CI 3.9, 18.8) were islet autoantibody-positive. TGA-IgA prevalence was 3.5% (95% CI 2.7, 4.6) overall, with 3.2% (95% CI 2.3, 4.2) newly identified positivity among those without known coeliac disease. Capillary–venous sample concordance was high (85–95% across autoantibodies), increasing with antibody level from 66.7% to 100% across terciles. Venous LIPS to bridge-ELISA concordance ranged from 50% for GADA to 90% for other autoantibodies, with low-affinity GADA partially accounting for discrepancies. Islet autoantibody-positive individuals >15 years (measured by 3-screen solid-phase capture LIPS) had significantly higher median antibody levels than those ≤15 years (53.5 vs 19.3 arbitrary units, p=0.006). Coeliac disease autoantibody prevalence declined markedly with age from 9.1% (≤15 years) to 0.6% (>75 years) (p<0.001), contrasting with the more stable age distribution of islet autoantibodies.

Conclusions/interpretation Population-wide autoimmunity screening across all age groups is feasible using minimally invasive capillary sampling and advanced immunoassay technology. The substantial prevalence of autoimmunity in clinically unaffected individuals (2.3% for islet autoantibodies, 3.2% for coeliac disease autoantibodies) suggests significant opportunities for earlier detection and intervention. Age-related differences in antibody levels and the detection of multiple autoantibodies in adults without diabetes warrant longitudinal follow-up to understand natural history and progression risk in older populations.

Keywords Autoantibodies · Autoimmunity · Capillary blood sampling · Coeliac disease · General population screening · Luciferase immunoprecipitation system (LIPS) · Population-based study · Tissue transglutaminase antibodies · Type 1 diabetes · UNISCREEN study

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Extended author information available on the last page of the article.

Abbreviations

AU	Arbitrary units
CLIA	Chemiluminescence immunoassay
IASP	Islet Autoantibody Standardization Program

Research in context

What is already known about this subject?

- Type 1 diabetes and coeliac disease autoantibodies can be detected years before clinical onset, with screening programmes primarily focused on paediatric populations
- Multiple islet autoantibodies in children predict 90% of progression to type 1 diabetes within 15 years, but adult autoantibody significance remains less well defined
- Traditional assay methods requiring larger blood volumes and longer processing times have limited population-wide implementation

What is the key question?

- Can a new, minimally invasive screening method using capillary blood sampling and advanced technology effectively detect autoantibodies across all age groups?

What are the new findings?

- Novel solid-phase capture luciferase immunoprecipitation system technology requiring only 1 µl of serum achieved high concordance with traditional methods
- Islet autoantibody prevalence was 2.3% in individuals without diabetes, with high antibody levels and multiple autoantibody positivity also in older individuals
- Coeliac disease autoantibody prevalence was 3.2% in individuals without disease and declined with age

How might this impact on clinical practice in the foreseeable future?

- This study demonstrates that population-wide autoimmunity screening using minimally invasive methods is feasible and acceptable, potentially enabling earlier detection and intervention strategies, improved disease classification and more personalised treatment approaches across all age groups, rather than being limited to paediatric populations

LIPS	Luciferase immunoprecipitation system
scLIPS	Solid-phase capture luciferase immunoprecipitation system
tGADA	GADA measured using an N-terminally truncated GAD65
TGA-IgA	Tissue transglutaminase autoantibodies of the IgA class

Introduction

Type 1 diabetes and coeliac disease are autoimmune conditions with specific autoantibodies detectable years before clinical onset. Though historically viewed as paediatric disorders, both affect individuals across all age groups, with variable presentations and progression rates [1–3].

Early detection is crucial for preventing complications and modifying prognosis. For type 1 diabetes, benefits include reducing diabetic ketoacidosis at diagnosis [4], minimising symptoms [5] and enabling disease-modifying therapies [6]. For coeliac disease, early detection identifies silent cases, enabling treatment and preventing complications including malabsorption, nutritional deficiencies and increased malignancy risk [7].

Disease-specific autoantibodies serve as reliable biomarkers for both conditions. For type 1 diabetes, these include GADA, IAA, IA-2A and ZnT8A [8]. Multiple islet autoantibodies significantly increase progression risk, approaching 90% within 15 years in children and adolescents [9, 10], though prediction is less clear in adults where the clinical significance of autoantibody positivity remains less defined [11–14]. For coeliac disease, tissue transglutaminase autoantibodies of the IgA class (TGA-IgA) is the primary serological marker.

While paediatric screening programmes demonstrated feasibility and benefit [15], comprehensive prevalence data across all age groups remain limited [1, 11]. To address these gaps, we conducted the UNISCREEN study in Cantalupo, Milan, Italy [16, 17], screening 1532 residents aged 1–100 years using solid-phase capture luciferase immunoprecipitation system (scLIPS) technology, representing a significant methodological advancement over traditional approaches. The

3-screen scLIPS assay requires just 1 µl of serum to simultaneously test for GADA, IA-2A and ZnT8A [18], a 25-fold reduction compared with conventional diagnostic assays, with faster processing (4 vs 23 h) and fewer procedural steps. This dramatic reduction in sample volume requirements makes minimally invasive capillary blood collection practical for population screening, potentially increasing participation rates, particularly in paediatric populations where venepuncture presents a significant barrier. Our primary objective was to validate the feasibility of minimally invasive sampling combined with novel antibody tests for population-wide screening of type 1 diabetes and coeliac disease autoantibodies. Secondary aims included determining the prevalence and age-related distribution of type 1 diabetes and coeliac disease autoantibodies across the full age spectrum, with particular focus on adults where comprehensive data remain limited.

Methods

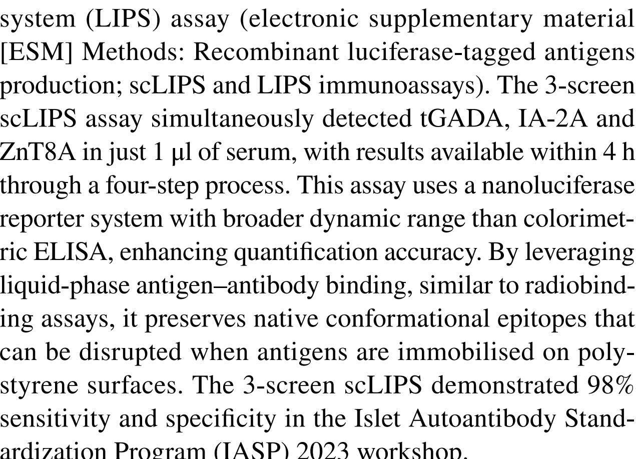
Study design and population The UNISCREEN study took place in Cantalupo, a village in the Cerro Maggiore municipality, Milan, Italy, with a population of 3061 residents aged 0–100 years. The study was approved by the San Raffaele Hospital Ethics Committee and registered on ClinicalTrials.gov (registration no. NCT05841719); the detailed methodology is available in previous publications [16, 17].

Following a public awareness campaign through schools, community centres, social media and mailings, residents aged 1–100 years were invited to participate voluntarily. Recruitment occurred between 22 April 2023 and 29 October 2023. Non-residency was the only exclusion criterion. Demographic information, including participant sex, was obtained by self-report during the screening interview and recorded in the case report form. Race/ethnicity data were not collected as the study was conducted in a geographically homogeneous Northern Italian population with limited racial/ethnic diversity.

Adult participants provided written informed consent, while parents or guardians consented on behalf of minors. The study adhered to the principles of the 2013 Declaration of Helsinki [19].

Serum sample collection Trained nurses and physicians collected capillary blood samples from each participant via fingerprick. If the sample was insufficient, the procedure was repeated. The blood was collected in microtubes (Microvette 200 Z tubes, Sarstedt, Numbrecht, Germany), centrifuged and then transferred to fresh tubes for storage at −20°C.

Type 1 diabetes autoantibody screening All capillary serum samples were analysed using two assays: a novel 3-screen scLIPS assay and an IAA luciferase immunoprecipitation



system (LIPS) assay (electronic supplementary material [ESM] Methods: Recombinant luciferase-tagged antigens production; scLIPS and LIPS immunoassays). The 3-screen scLIPS assay simultaneously detected tGADA, IA-2A and ZnT8A in just 1 µl of serum, with results available within 4 h through a four-step process. This assay uses a nanoluciferase reporter system with broader dynamic range than colorimetric ELISA, enhancing quantification accuracy. By leveraging liquid-phase antigen–antibody binding, similar to radiobinding assays, it preserves native conformational epitopes that can be disrupted when antigens are immobilised on polystyrene surfaces. The 3-screen scLIPS demonstrated 98% sensitivity and specificity in the Islet Autoantibody Standardization Program (IASP) 2023 workshop.

The IAA LIPS assay, performed separately due to technical limitations, used a competitive binding format with nanoluciferase-tagged insulin and unlabelled insulin (Actrapid, NovoNordisk, Denmark) to measure IAA levels [20–22]. This assay demonstrated 54.0% sensitivity and 100% specificity in IASP 2023. The technical constraints that prevented incorporating IAA into the multiplex scLIPS assay included: different buffer requirements, low IAA levels that would be masked by other antibodies and the need for competitive binding to minimise nonspecific signals.

Single autoantibody testing on capillary samples To determine antigen specificity, capillary samples testing positive in 3-screen scLIPS underwent individual LIPS assays for each autoantibody. GADA was measured using N-terminally truncated GAD65 antigen (tGADA) to improve specificity by targeting disease-associated epitopes in the middle and C-terminal regions while excluding nonspecific N-terminal binding [22–26]. Competition with unlabelled truncated GAD65 distinguished high-affinity antibodies from low-affinity responses that carry lower diabetes risk [27]. IA-2A was detected using the intracellular domain of IA-2, which contains the major antigenic determinants recognised in type 1 diabetes [28]. ZnT8A employed a dimeric construct linking the C-terminal domains containing R325 and W325 variants, enabling simultaneous detection of autoantibodies to both major polymorphic forms [29]. IAA used nanoluciferase-tagged insulin with competition by unlabelled insulin to eliminate nonspecific binding and identify high-affinity autoantibodies associated with diabetes progression [20, 30]. These assays showed the following performance characteristics in the IASP 2023 workshop: tGADA (86% sensitivity, 98% specificity), IA-2A (78% sensitivity, 100% specificity), ZnT8A (76% sensitivity, 100% specificity) and IAA (54% sensitivity, 100% specificity).

Coeliac disease screening All samples underwent initial screening using the LIPS assay, which uses a recombinant transglutaminase–nanoluciferase fusion protein to detect TGA-IgA. This approach requires minimal serum volume

(1 µl) and demonstrates high analytical performance, with sensitivity >95% and specificity >97% in internal comparison studies with reference radiobinding and ELISA assays.

Confirmatory testing in venous samples and assay format comparison To confirm the presence of antibodies, venous samples were requested from antibody-positive individuals. Confirmatory testing of islet antibodies involved re-measuring antibody levels using single-antibody LIPS assays and performing bridge-ELISA tests for GADA, IA-2A and ZnT8A. We then compared the concordance between these assays. For participants who tested positive on the 3-screen scLIPS assay, we applied a modified IAA threshold and adopted a Bayesian-informed approach similar to that in the Fr1da study (described in abstract 21 of the proceedings of the 61st EASD Annual Meeting of the EASD [31]). A more detailed explanation of assay conduction is provided in the ESM Methods (Detailed autoantibody measurement procedures).

Confirmatory testing of coeliac disease antibodies involved re-measuring TGA-IgA and tissue transglutaminase IgG (TGA-IgG) autoantibodies by LIPS and by direct ELISA (Eu-tTG IgA and Eu-tTG IgG, Eurospital, Trieste, Italy), chemiluminescence immunoassay (CLIA) for TGA-IgA on a BIO-FLASH platform (QUANTA Flash h-tTG IgA, Inova Diagnostics, San Diego, USA) and measuring anti-endomysial antibodies by indirect immunofluorescence using a Monkey oesophagus kit (NOVA Lite, Werfen, Barcelona, Spain) (ESM Methods: Other assays).

The methodology for autoantibody threshold selection is described in the ESM Methods (Characteristics of autoantibody distributions and threshold selection) and visualised in ESM Fig. 1.

Statistical analyses Descriptive statistics were calculated for age distribution and antibody prevalence. Between-group comparisons of antibody prevalence across age groups were conducted using χ^2 tests. The 95% CIs were calculated and reported for estimates. Statistical significance was set at $p<0.05$, and all tests were two-tailed.

This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies. Statistical analyses were performed using R version 4.5.1 (https://cran.r-project.org/).

Results

Study feasibility A total of 1535 residents agreed to participate in the study, representing 50.1% of the eligible Cantalupo population [16]. Capillary blood serum adequate for autoantibody testing was collected from 1532 participants by fingerprick performed by trained nurses and physicians. A single fingerprick was sufficient in 47.1% of participants, while 52.9% required ≥2 fingerpricks.

Questionnaire responses demonstrated high acceptability of the screening programme, with over 99% of participants supporting systematic screening for diabetes, coeliac disease and cardiovascular diseases. Initial concerns about capillary blood sampling (9.7% of adults, 21.9% of parents) were substantially reduced post screening, with over 95% finding the procedure practical and preferring it over venous sampling [16]. Psychological concerns about potential disease diagnosis also decreased after screening (from 24.0% to 21.3% in adults, 31.7% to 23.4% in parents). Overall satisfaction was high, with statistically significant increases in positive responses observed after screening ($p<0.001$).

Cohort characteristics This cohort comprised 55.0% female and 45.0% male participants, with mean age 46.0 years (IQR 26.9–64.4). Most participants (94.9%) had no diabetes, 0.3% had type 1 diabetes and 4.8% had type 2 diabetes; 1.0% had coeliac disease (Table 1). Comparison with census data showed age and sex distributions similar to the wider municipality area (ESM Fig. 2). Response rates varied by age group ($p<0.001$), with highest participation in children/early adolescents aged 1–15 years (58.7%) and lower rates in adolescents and young adults 16–30 years (41.3%) and older adults >75 years (42.8%) [16].

Islet autoantibody screening in population without diabetes Among 1454 individuals without known diabetes, 31 (2.1%; 95% CI 1.5, 3.0) tested positive using 3-screen scLIPS, and two (0.1%; 95% CI 0.0, 0.5) tested positive for IAA only. Overall islet autoantibody prevalence was 2.3% (33/1454; 95% CI 1.6, 3.2) (Table 1, Fig. 1a–d, ESM Tables 1, 2).

Single autoantibody testing on capillary samples To determine antigen specificity, the same capillary samples that tested positive in 3-screen scLIPS (*n*=36) were retested using individual LIPS assays for each autoantibody (Fig. 2a, b). tGADA was detected in 30 samples (30/36, 83.3%) by single LIPS, which decreased to 16 (16/36, 44.4%) after competition with unlabelled antigen. Competition-eliminated samples had lower median screening values (24.4 arbitrary units [AU]) than confirmed positives (88.7 AU). Other specificities included IA-2A in six samples (6/36, 16.6%), ZnT8A in seven samples (7/36, 19.4%) and IAA in six samples (6/36, 16.7%) using an adjusted threshold. Two samples (2/36, 5.6%) tested negative for all individual autoantibodies.

Among the 34 autoantibody-positive individuals in single LIPS assays, 24 (24/34, 70.6%) had a single autoantibody and ten (10/34, 29.4%) had multiple autoantibodies, representing 1.6% and 0.6% of the total population, respectively.

Table 1 Characteristics of study participants at screening: demographics, clinical parameters and autoantibody profile

Characteristic	Overall N=1532	No diabetes N=1454	Type 1 diabetes N=5	Type 2 diabetes N=73	p value
Age, years	46.0 ± 23.1	44.6 ± 22.8	54.9 ± 23.0	72.7 ± 8.7	<0.001
Female sex	843 (55.0)	810 (55.7)	2 (40.0)	31 (42.5)	0.068
BMI, kg/m^2	23.4 ± 4.8	23.3 ± 4.8	25.6 ± 4.4	26.4 ± 4.5	<0.001
BMI ≥30 kg/m^2[a]	124 (8.3)	110 (7.7)	1 (20.0)	13 (17.8)	0.006
HbA_{1c}, mmol/mol	36.3 ± 6.0	35.5 ± 4.1	72.2 ± 15.3	50.0 ± 11.1	<0.001
HbA_{1c}, %	5.5 ± 0.6	5.4 ± 0.4	8.7 ± 1.4	6.7 ± 1.0	<0.001
HbA_{1c} ≥48 mmol/mol (≥6.5%)	52 (3.4)	10 (0.7)	5 (100.0)	37 (50.7)	<0.001
Diabetes therapy[b]					<0.001
No	11 (14.1)	0 (0.0)	0 (0.0)	11 (15.1)	
Insulin	9 (11.5)	0 (0.0)	4 (80.0)	5 (6.8)	
Other	53 (67.9)	0 (0.0)	0 (0.0)	53 (72.6)	
Insulin plus others	5 (6.4)	0 (0.0)	1 (20.0)	4 (5.5)	
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
History of gestational diabetes	26 (1.7)	24 (1.7)	1 (20.0)	1 (1.4)	0.007
3-Screen scLIPS positive (AU ≥15)	36 (2.3)	31 (2.1)	1 (20.0)	4 (5.5)	0.006
IAA LIPS positive (AU ≥0.55)	9 (0.6)	2 (0.1)	4 (80.0)	3 (4.1)	<0.001
3-Screen scLIPS or IAA positive	44 (2.9)	33 (2.3)	4 (80.0)	7 (9.6)	<0.001
TGA-IgA LIPS positive	54 (3.5)	54 (3.7)	0 (0.0)	0 (0.0)	0.219
Confirmed coeliac disease	16 (1.0)	15 (1.0)	1 (20.0)	0 (0.0)	<0.001

Data are presented as mean ± SD or n (%). p values are from Kruskal–Wallis test for continuous variables or χ^2 test for categorical variables comparing across diabetes status groups

[a]BMI data were missing for 34 participants

[b]Percentages refer to the 78 participants with diabetes

The most common pattern was tGADA-only (21/34, 61.8%). The multiple autoantibody-positive samples comprised various combinations, including all four autoantibodies (tGADA, IA-2A, ZnT8A and IAA, two individuals), three antibodies (tGADA, IAA and ZnT8A, one individual) or two antibodies (tGADA with IA-2A, ZnT8A or IAA, two individuals each; IAA and ZnT8A, one individual).

Validation of islet autoantibodies in venous samples Positive individuals identified during screening were recontacted, and 20 provided venous samples. When venous samples were retested using LIPS, all 20 individuals remained autoantibody-positive. The concordance between capillary and venous LIPS results was 90% for tGADA, 95% for IAA, 90% for ZnT8A and 85% for IA-2A (Fig. 2b).

Concordance between assay formats increased with antibody level. When samples were stratified by screening value into terciles, capillary-to-venous LIPS concordance increased from 66.7% (lowest tercile) to 100% (highest tercile) for most autoantibodies (ESM Table 3). Venous LIPS-to-bridge-ELISA concordance similarly increased across terciles, ranging from 33.3% to 100% depending on the autoantibody (ESM Table 4).

Discrepancies between methods occurred predominantly for GADA, the most prevalent islet autoantibody in this cohort. Overall concordance between venous LIPS and bridge-ELISA was only 50% for GADA, compared with 75–90% for other autoantibodies. The high concordance observed for IAA, ZnT8A and IA-2A, even in lower terciles, reflects that most samples were negative for these antibodies. Low-affinity GADA detected by LIPS but not by bridge-ELISA partially explains the observed discrepancies, as evidenced by improved concordance (75%) with the GADA competition assay.

Age-related patterns of islet autoantibodies Islet autoantibody prevalence suggests a potentially bimodal pattern: 3.1% in children/early adolescents ≤15 years, 1.6% in adolescents and young adults 16–30 years, 1.5% in adults 31–45 years, 0.8% in middle-aged adults 46–60 years, 4.0% in seniors 61–75 years and 3.8% in older adults >75 years (trend p=0.15) (Fig. 3c, ESM Table 5).

Among autoantibody-positive individuals, those >15 years (n=29) had significantly higher median antibody levels (53.5 AU, range 15.3–1375.1) than those ≤15 years (n=7; median 19.3 AU, range 16.1–21.6) (p=0.006) (Fig. 3a–c),

Fig. 1 Distribution of autoantibodies in capillary blood samples. Frequency histograms (**a**, **c**, **e**) and box plots with individual values (**b**, **d**, **f**) show autoantibody levels. (**a**, **b**) Combined tGADA/IA-2A/ZnT8A scLIPS assay (cut-off: 15 AU, dashed line), with points coloured by diabetes status: type 1 diabetes (T1D, red); type 2 diabetes (T2D, blue); no diabetes (transparent). (**c**, **d**) IAA assay (cut-off: 0.55 AU, dashed line), coloured by diabetes status. (**e**, **f**) TGA-IgA assay, coloured by coeliac disease (CD) status (CD: magenta; no CD: transparent), with cut-offs for positive (6 AU) and borderline (3.5 AU) results indicated by dashed lines. Grey areas denote borderline regions

Fig. 2 Distribution of autoantibodies in screening and confirmatory testing for type 1 diabetes and coeliac disease. Lollipop plots show antibody levels in individuals autoantibody positive at the screening stage in ascending order of AU in screening assays (**a**, **c**), coloured by disease status: type 1 diabetes (T1D, red), type 2 diabetes (T2D, blue), no diabetes (transparent) for panel (**a**); coeliac disease (CD, magenta), no CD (transparent) for panel (**c**). Individual ID numbers below (**b**) and (**d**) also correspond to (**a**) and (**c**), respectively. Dashed lines show cut-offs for positivity (**a**, **c**) or tenfold the threshold (**c**). Tilemaps compare single-antibody assay score concordance across assay formats and capillary or venous sample types (**b**, **d**), with colours indicating positive (orange), borderline (yellow), negative (blue) and not tested or unavailable venous samples (grey). Comp, competition with unlabelled antigen; IFA, immunofluorescence assay

reflecting differences in both autoantibody profiles and individual antibody levels between age groups. This difference was specific to positive individuals, as autoantibody-negative groups showed no age-related difference in assay background (p=0.71).

Islet autoantibodies in type 2 diabetes Among 73 individuals with type 2 diabetes, seven (9.6%; 95% CI 3.9, 18.8) had islet autoantibodies (Table 1, ESM Table 2). Excluding individuals with IAA-only positivity on insulin therapy, since the IAA interpretation is confounded, prevalence of islet autoantibodies was 7.8% (5/64; 95% CI 3.4, 17.0). These individuals showed no significant differences in age, BMI and HbA_{1c} compared with autoantibody-negative individuals with type 2 diabetes (ESM Table 6).

Coeliac disease autoantibody screening Of 1532 individuals screened, 54 (3.5%; 95% CI 2.7, 4.6) tested positive for TGA-IgA (>6 AU), with 14 additional borderline results (0.9%; 95% CI 0.5, 1.5) (Fig. 1e, f, Table 1, ESM Table 7). Excluding 16 individuals with known coeliac disease, 48 of 1516 (3.2%; 95% CI 2.3, 4.2) were newly identified as positive. Of the newly identified positives, 25 (1.6%; 95% CI 1.01, 2.29) had TGA-IgA levels ≥60 AU (more than tenfold the cut-off), meeting the European Society for Paediatric Gastroenterology Hepatology and Nutrition diagnostic criteria for coeliac disease [32].

Assay concordance of coeliac disease autoantibodies by antibody level Twenty-four positive individuals provided venous samples for confirmatory testing. Concordance between assay formats varied by initial antibody level (Fig. 2c, d). For high positive results (≥60 AU), LIPS confirmed 100% of individuals, followed by ELISA at 86.4%, CLIA at 81.8% and immunofluorescence at 68.2%. Among intermediate levels (20–60 AU, n=8), only LIPS maintained 100% confirmation while other methods ranged from 37.5% to 62.5%. For low positive results (6–20 AU, n=5), LIPS confirmed 80% whereas other methods confirmed 40% or less.

Age-related pattern of TGA-IgA antibodies The prevalence of TGA-IgA showed a striking age-related decline: 9.1% (95% CI 5.8, 14.0) among those ≤15 years, 3.9% (95% CI 1.7, 8.2) in the 16–30 years age group, 4.5% (95% CI 2.5, 8.0) among those 31–45 years, 3.0% (95% CI 1.6, 5.4) in the 46–60 years age group, 0.9% (95% CI 0.2, 2.9) among those 61–75 years and 0.6% (95% CI 0.0, 4.0) in individuals >75 years (χ^2 trend p<0.001) (Fig. 3e, f, ESM Table 5). This age-related pattern persisted even after excluding individuals with known coeliac disease.

Discussion

Our population-based screening demonstrates the feasibility and potential value of comprehensive autoimmunity screening across all age groups using minimally invasive capillary blood sampling combined with advanced immunoassay technologies. The study provides valuable insights into both the methodological requirements for population-wide screening and the prevalence and distribution of type 1 diabetes and coeliac disease autoantibodies in a general Northern Italian population spanning from childhood to advanced age.

The feasibility of large-scale autoantibody screening has been enhanced by advances in immunoassay technology. A notable methodological advancement in our study was the use of the novel high-throughput, plate-based scLIPS assay, which requires only 1 μl of serum to test for three islet autoantibodies.

Our screening programme used a two-stage autoantibody approach similar to the Fr1da study [15], but with key differences. The Fr1da study screened capillary blood samples from children using a commercial 3-screen ELISA, retesting samples above the 97.5th percentile with reference radiobinding assays, with venous blood testing confirming autoantibody status in children with at least two positive autoantibodies. This two-stage design was implemented to balance screening efficiency with diagnostic accuracy: the ELISA serves as a high-throughput first-line screening tool, while radiobinding assays, considered the reference standard with superior specificity, are used for confirmation and precise autoantibody quantification to determine the number of positive autoantibodies and stratify type 1 diabetes risk [33]. Notably, the Fr1da study did not include IAA testing in the initial screening for all children, reserving it instead for those already positive for other autoantibodies. The commercial 3-screen bridge-ELISA used in Fr1da requires larger sample volumes (25 μl) and longer processing times (23 h vs 4 h for our scLIPS), with more procedural steps (eight vs four). Unlike Fr1da, we included IAA as a frontline test in our initial screening panel, enabling more comprehensive autoantibody profiling. Additionally, we employed a truncated tGADA assay to improve specificity [23, 25].

This method demonstrated excellent performance compared with traditional ELISA approaches in both capillary and venous samples. The high concordance between capillary and venous samples (85–100%) validates the use of minimally invasive capillary blood collection for initial screening, potentially increasing participation rates in future screening initiatives. These findings align with our previously reported feasibility and acceptability data, where 87.5% of adults and 92.0% of children's parents preferred capillary blood sampling over venous sampling

Fig. 3 Age distribution, autoantibody profiles and prevalence rates in population screening for type 1 diabetes and coeliac disease. Age distribution histogram of screened individuals (**a**). Lollipop plots of autoantibody screening assay AU showing autoantibody-positive individuals arranged by age (*x*-axis) (**b**, **d**, **e**). Diabetes status is indicated by shape: type 1 diabetes (T1D) as diamonds, type 2 diabetes (T2D) as squares and no diabetes as circles (**b**, **d**). Islet autoantibody combinations as ascertained by single LIPS assays in capillary samples are shown by colour (**b**, **d**). Coeliac disease (CD) status is shown by colour: CD in magenta and no CD transparent (**e**). Dashed lines show cut-offs for positivity (**b**, **d**, **e**) or tenfold the threshold (**e**). Bar plots of 3-screen islet autoantibody or TGA-IgA prevalence across the indicated age groups (**c**, **f**). For CD, autoantibody prevalence is shown as observed (orange) or adjusted by adding already known CD cases (green). Ab+, autoantibody-positive

a
Individuals (*n*)
Age (years)

b
3-Screen scLIPS (AU)
Age (years)
GADA + IA-2A + ZnT8A + IAA
GADA + IA-2A
GADA + ZnT8A + IAA
GADA + ZnT8A
GADA + IAA
ZnT8A + IAA
IA-2A only
ZnT8A only
GADA only
Unconfirmed

c
Prevalence (%)
≤15 16–30 31–45 46–60 61–75 >75
Age groups (years)

d
IAA LIPS (AU)
Age (years)
No diabetes
T1D
T2D
GADA + IA-2A + ZnT8A + IAA
GADA + IAA
No other antibodies

e
TGA-IgA LIPS (AU)
Age (years)
No CD
CD

f
Prevalence (%)
≤15 16–30 31–45 46–60 61–75 >75
Age groups (years)
Prevalence
Adjusted (Ab+ & known CD)
Observed Ab+

[16], a rate similar to that demonstrated in recent Swedish studies for home-based capillary sampling [34].

Our concordance analysis stratified by initial antibody level provides guidance for screening programme design. Since assay format agreement increased substantially with higher antibody levels, different confirmation strategies may be appropriate based on initial screening results. For islet autoantibodies, agreement increased from 55% in the lowest tercile to 85% in the highest tercile, and for coeliac disease autoantibodies from less than 40% for antibody levels <20 units to more than 80% for levels >60 units (approximately ten times the threshold). These data suggest that low-titre positives require careful interpretation considering clinical context and multiple autoantibody positivity, and possibly require longitudinal follow-up rather than immediate intervention, given the lower confirmation rates across assay platforms at lower antibody levels.

We identified islet autoantibody positivity in 2.3% of individuals without known diabetes, with 27.3% of positives having multiple autoantibodies. This prevalence is higher than our previous work in Northern Italy in the 1990 Cremona study, which found 1% of adults with normal glucose tolerance had GADA positivity [35]. Several factors may explain this: more comprehensive screening testing for all four major islet autoantibodies rather than focusing primarily on GADA and IA-2A, more sensitive assay technology and a broader age range, capturing age groups with potentially higher autoantibody prevalence.

The detection of multiple islet autoantibodies in some general population adults without clinical diabetes represents an intriguing finding. In children, the presence of multiple islet autoantibodies establishes stage 1 type 1 diabetes diagnosis [8], with 90% risk of progression to clinical disease within 15 years [9, 10]. However, progression rates in adults with multiple autoantibodies appear substantially slower and more variable [11–14]. Our prior Cremona study found that none of the adults with GADA or IA-2A and normal glucose tolerance developed diabetes over 8 years of follow-up [35], and the SNAIL study documented individuals who remained diabetes-free for at least 10 years despite multiple islet autoantibodies [11]. Continuing longitudinal follow-up of older general population adults with multiple islet autoantibodies identified in our study may yield valuable insights into the natural history of islet autoimmunity when progression is slow or absent, immunologic or metabolic features associated with non-progression and potential biomarkers predicting which adults with autoimmunity will progress vs remain stable.

One of our most striking observations was the significantly higher islet autoantibody levels in post-adolescent positive individuals compared with pre-pubertal individuals (median 53.5 vs 19.3 AU, p=0.006), with a 64-fold difference in maximum values. This finding has important implications for risk stratification. Buzzetti et al previously identified a bimodal distribution of GADA levels in late-onset autoimmune diabetes, demonstrating that individuals with high GADA levels had more prominent insulin deficiency and more severe autoimmunity compared with those with low GADA levels [13]. Although our study differs in examining pre-clinical screening rather than diagnosed diabetes, the observation of age-related differences in antibody levels suggests that antibody level stratification might be valuable not only in clinical diabetes classification but also in screening contexts. Current staging criteria for presymptomatic type 1 diabetes [8] do not account for age-related differences in antibody levels, applying the same thresholds from childhood to adulthood. Our findings suggest that age-specific thresholds or age-adjusted risk stratification algorithms might improve accuracy of progression prediction, though prospective longitudinal studies are needed to determine whether age-specific antibody level thresholds improve risk prediction.

Unlike most screening programmes that reserve IAA testing for individuals already positive for other autoantibodies [15], we included frontline IAA screening for all participants. This comprehensive approach had limited incremental yield, identifying only one additional participant (0.1% of total screened) beyond what would have been detected by 3-screen scLIPS alone. However, IAA testing did provide valuable antibody characterisation for individuals already identified as 3-screen positive. The interpretation of IAA is particularly challenging in insulin-treated individuals, as exogenous insulin exposure can induce antibodies mechanistically distinct from those in autoimmune diabetes. To improve cost-effectiveness in future screening programmes, our data suggest reserving IAA testing for individuals already positive for other islet autoantibodies, while maintaining comprehensive antibody characterisation in relevant cases, or including frontline IAA screening primarily in children where IAA-only positivity is more common and clinically relevant.

The detection of islet autoantibodies in 7.8% of insulin-naive individuals with clinically diagnosed type 2 diabetes aligns with previous Italian studies [13, 36] and supports the value of autoantibody testing for improving diabetes classification. The predominance of GADA in autoantibody-positive adults aligns with prior findings reporting GADA as the dominant marker in adult-onset autoimmune diabetes [36], with multiple autoantibodies being less prevalent with increasing age of onset. Accurate diabetes classification has important clinical implications, as individuals with autoimmune diabetes typically require earlier insulin therapy and may benefit from different treatment approaches compared with those with type 2 diabetes.

For coeliac disease autoimmunity, we identified TGA-IgA positivity in 3.2% of individuals without known coeliac disease, identifying substantial undiagnosed autoimmunity that warrants clinical follow-up. This prevalence notably exceeds the 0.4% we observed in the 1990 Cremona study using radiobinding assay [37], possibly reflecting improved assay sensitivity, genuine increase in coeliac disease prevalence over the past three decades or different age distributions between cohorts. The striking inverse relationship between coeliac disease autoantibody prevalence and age (declining from 9.1% in children or early adolescents to 0.6% in older adults, $p<0.001$) contrasts markedly with the more stable age distribution of islet autoantibodies. This pattern might reflect generational differences in gluten exposure or other environmental risk factors, increased clinical diagnosis and treatment in younger generations due to heightened awareness, potential development of oral tolerance to gluten in some individuals over time or differential survival rate related to untreated coeliac disease complications in older generations. Unlike type 1 diabetes screening where the role in adults remains debated, the clinical benefits of identifying undiagnosed coeliac disease in adults are well-established. Untreated coeliac disease, even when asymptomatic, carries risk of malabsorption, nutritional deficiencies, osteoporosis and malignancy risk [7], supporting the value of coeliac disease screening across all age groups.

Several limitations must be acknowledged. Our study was designed primarily to demonstrate feasibility rather than provide definitive prevalence estimates. Despite recruiting 50% of the target population, self-selection bias cannot be excluded, though our demographic similarity to the overall Cerro Maggiore population suggests reasonable representativeness. Participation rates varied by age group, with lower rates among adolescents/young adults (38.4%) and older adults (42.6%) compared with other groups (52–58%), likely reflecting work commitments or mobility limitations rather than health-related selection bias. The cross-sectional design precludes assessment of autoantibody development or progression to clinical disease in this report, though longitudinal follow-up is planned. Although sex-stratified analyses were not performed due to the feasibility focus and limited sample sizes in autoantibody-positive subgroups, the balanced sex distribution (55% female, 45% male) representative of the general population supports generalisability of findings to both sexes. Our study population from a single Northern Italian district may not be representative of other geographical regions or ethnic groups. The limited number of individuals with diagnosed type 1 diabetes (n=5) and coeliac disease (n=16) restricts precision of estimates for assay sensitivity in established disease.

Our comprehensive population-based screening study demonstrates the feasibility and potential value of autoimmunity screening across all age groups using minimally invasive capillary blood sampling and advanced immunoassay technologies. The substantial prevalence of autoimmunity in clinically unaffected individuals (2.3% for islet autoantibodies, 3.2% for coeliac disease autoantibodies) suggests significant opportunities for earlier intervention, improved disease classification and more personalised treatment approaches. The detection of multiple islet autoantibodies in some general population adults warrants further investigation to understand factors associated with slow or absent progression to clinical disease. While further research is needed to establish clinical significance of autoantibody positivity in different age groups, optimal screening strategies and cost-effectiveness, our findings provide important foundational data for developing evidence-based, age-appropriate screening programmes that could ultimately reduce the burden of these important autoimmune conditions.

Supplementary Information The online version contains peer-reviewed but unedited supplementary material available at https://doi.org/10.1007/s00125-026-06680-y.

Acknowledgements We thank the population from Cantalupo for their generous participation, the Municipal Authorities, the physicians of the UNISCREEN Study Group from San Raffaele University (listed in [16]), the participant nurses and the volunteers from Fondazione Italiana Diabete, local Civil Protection, Red Cross and Rotary Club for their professional, enthusiastic and continuous support throughout the study. This manuscript was prepared with the assistance of Claude 4.5 sonnet, a large language model, for drafting, language editing, statistical analysis code generation and editing. The authors acknowledge the use of this AI technology and have reviewed and validated the content to ensure its accuracy and integrity. The authors are solely responsible for the content and conclusions of this work.

Data availability The datasets generated and analysed during the current study are not publicly available due to privacy and ethical restrictions, as they contain sensitive health information from a small, identifiable community. However, anonymised data are available from the corresponding authors upon reasonable request, subject to approval by the Ethics Committee of San Raffaele Hospital, Milan, Italy, and completion of appropriate data sharing agreements.

Funding The UNISCREEN Study was conducted in collaboration with Fondazione Italiana Diabete (FID), Milan, Italy, which provided financial support (FID grant 07/2023) and operational contributions including coordination of the public information campaign, organisation of fieldwork logistics for sample collection and procurement of sample collection materials. Islet autoantibody LIPS immunoassays were developed with the support of Breakthrough T1D (Grant Keys: 2-SRA-2015-50-Q-R, 2-SRA-2018-534-S-B, 2-SRA-2020-964-S-B) and the Leona M. and Harry B. Helmsley Charitable Trust (Grant Key: 2-SRA-2015-50-Q-R).

Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement All authors have contributed substantially to the study in terms of conception or design, data acquisition, analysis or interpretation, and have critically reviewed the manuscript for important intellectual content. All authors approved the article in its final version. In detail: IM drafted the manuscript and conducted data

analyses and interpretation; CB was responsible for autoantibody measurements and initial data analysis; E. Bazzigaluppi was responsible for autoantibody measurements and initial data analysis; SM, AL, GA, SA, E. Borgonovo, AS, GP and MM contributed to data collection and evaluation; FU contributed to data collection and evaluation and project administration; KG contributed to assay development, validation and manuscript editing; PA contributed to assay development, validation, threshold selection and manuscript editing; WH contributed to assay development, validation and manuscript editing; VL supervised autoantibody measurements, conducted data analyses and interpretation, and contributed to manuscript drafting and editing; E. Bosi conceived, designed and oversaw the study, participated in person to screening procedures, wrote the study protocol and participated in drafting and editing the final manuscript. E. Bosi is responsible for the integrity of the work as a whole.

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