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Low C-peptide together with a high glutamic acid decarboxylase autoantibody level predicts progression to insulin dependence in latent autoimmune diabetes in adults: The HUNT study

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Abstract

Aim: To search for risk factors that could predict progression in latent autoimmune diabetes in adults (LADA) and compare them with those for type 2 diabetes.

Materials and Methods: This study included 175 participants with LADA (autoantibody positive, without insulin treatment ≥1 year after diagnosis) and 2331 participants with type 2 diabetes (autoantibody negative, without insulin treatment ≥1 year after diagnosis) from the HUNT2 and HUNT3 surveys. We used Cox regression models and receiver operating characteristic curve analysis to identify predictive factors for progression to insulin dependency within 10 years.

Results: Low C-peptide levels (<0.3 nmol/L) predicted progression to insulin dependency within 10 years in both LADA (hazard ratio [HR] 6.40 [95% CI, 2.02-20.3]) and type 2 diabetes (HR 5.01 [95% CI, 3.53-7.10]). In addition, a high glutamic acid decarboxylase autoantibody (GADA) level (HR 5.37 [95% CI, 1.17-24.6]) predicted progression in LADA. Together, these two factors had a discriminatory power between non-progressors and progressors of area under the curve (AUC) of 0.86 (95% CI, 0.80-0.93). In type 2 diabetes, younger age at diagnosis (<50 years: HR 2.83 [95% CI, 1.56-5.15]; 50-69 years: HR 2.11 [95% CI, 1.19-3.74]), high HbA1c levels (≥53 mmol/mol, HR 2.44 [95% CI, 1.72-3.46]), central obesity (HR 1.65 [95% CI, 1.06-2.55]) and a body mass index of more than 30 kg/m^2 (HR 1.73 [95% CI, 1.23-2.41]) were independent predictors. Together with C-peptide they reached an AUC of 0.79 (95% CI, 0.76-0.82).

Conclusion: Factors predicting progression to insulin dependence are partly similar and partly dissimilar between LADA and type 2 diabetes. A constellation of low C-peptide and high GADA levels identifies LADA patients who are probable to progress to insulin dependence.

KEYWORDS
population study, type 1 diabetes, type 2 diabetes

1 | INTRODUCTION

Patients with latent autoimmune diabetes in adults (LADA) share phenotypic features with both type 1 and type 2 diabetes. The risk of developing LADA is associated with overweight, physical inactivity and smoking, conditions which promote insulin resistance, as in type 2 diabetes.[1,2] However, development of LADA is specifically associated with autoantibodies for autoimmune diabetes, which are common in type 1 diabetes. Further, there is a genetic predisposition to development of LADA that is more similar to type 1 than to type 2 diabetes.[3]

Whereas risk factors for the development of LADA and for type 2 diabetes have been extensively studied, the factors associated with progression to insulin dependence have been less investigated. The clinical course of progression to insulin dependence is highly variable in LADA and type 2 diabetes. In general, patients with LADA progress faster to insulin dependence than patients with type 2 diabetes.[4] However, many LADA patients retain good metabolic control for many years with only diet or oral hypoglycaemic therapy. Factors influencing progression to insulin dependency in LADA have, however, only been partly elucidated; further, it is not known whether they are to some extent shared—as has been shown for development—with type 2 diabetes. A recent study pointed to an autoimmune genetic background by reporting that progression to insulin dependence was associated with a type 1 diabetes genetic risk score (T1D-GRS).[5] Regarding autoantibodies, some studies report that the degree of autoimmunity (a higher level of glutamic acid decarboxylase [GAD] autoantibodies) is associated with a need for insulin therapy[6,7] and serves as a good predictor for rapid insulin requirement in LADA,[5,8] while other studies have not supported this notion.[9-11] Data regarding a possible role of body weight are also discrepant. More studies are needed to clarify the relative importance, if any, of the factors mentioned.

The aim of this study was to identify factors that predict the progression to insulin dependence in LADA and compare them with those for type 2 diabetes. Further, to evaluate whether the predictive values of these factors are sufficiently strong to guide clinical decisions on treatment. To this end, we have used data from the all-population–based Trøndelag Health Study (HUNT) in Norway.

2 | MATERIALS AND METHODS

2.1 | Study population

The study was performed among participants from the Nord-Trøndelag region of the HUNT study in Norway. HUNT is a population-based study with information on approximately 120 000 adult participants (aged ≥20 years) collected during four cross-sectional surveys in 1984-1986 (HUNT1; n = 77 202, response rate 89.4%), 1995-1997 (HUNT2; n = 65 228, response rate 69.5%), 2006-2008 (HUNT3; n = 50 800, response rate 54.1%) and 2017-2019 (HUNT4; n = 56 042, response rate 54.0%). The surveys included questionnaires, clinical examinations and blood sampling. Details about HUNT are available elsewhere.[12,13]

We included participants with self-reported diabetes from the HUNT2 (n = 2028, prevalence 3.1%) and HUNT3 (n = 2264, prevalence 4.5%) surveys. The self-reported diagnosis of diabetes in HUNT has been validated.[14] Participants with diabetes in both HUNT2 and HUNT3 were included as a part of HUNT2 (Figure S1).

At the screening station, HUNT2 and HUNT3 participants with self-reported diabetes were given a more detailed diabetes-related questionnaire, which included questions on treatment (returned by 81% in both surveys). These participants were also invited to a clinical investigation (attended by 73% and 55%, respectively) that included measurements of HbA1c, fasting glucose, fasting C-peptide and autoantibodies against GAD (GADA) and Islet antigen-2 (IA-2A; this antibody was measured only in HUNT3). Almost all participants had blood samples stored as part of the main biological specimen assembled in HUNT2 or HUNT3. This made it possible to measure GADA in those with self-reported diabetes who did not attend the clinical investigation. Autoantibodies for IA-2 (if missing) and Zink transporter 8 (ZnT8A) were also measured separately in samples from all participants with diabetes who tested positive for GADA. GADA, IA-2A and ZnT8A were measured at the Hormone laboratory at Aker, Oslo University Hospital, Norway. Antibody levels were expressed as an antibody index relative to a standard serum, as described.[15] Cut-off levels for GADA, IA-2A and ZnT8A positivity were 0.08ai or higher, 0.11ai or higher and more than 0.08ai, respectively. The cut-off levels for GADA and IA-2A have 64% and 70% sensitivity, and 100% and 99% specificity, respectively, according to DASP participation in 2003. The cut-off level for ZnT8A had 46% sensitivity and 100% specificity from DASP 2010.

Participants were classified as LADA by being positive for GADA or IA-2A, and reported not having received insulin treatment within 1 year after their diagnosis. Participants were classified as type 2 diabetes if they were GADA negative (participants with IA-2A measurements available were classified as type 2 diabetes only if they were negative for IA-2A) and reported not being treated with insulin within 1 year after diagnosis (Figure S1).

Time to insulin dependence was calculated from age at diagnosis to age at insulin initiation and was censored at 10 years after diabetes diagnosis or at the latest available time point not on insulin (i.e. time of participation in HUNT2 or HUNT3) if earlier than 10 years. Data on diagnosis and insulin treatment were self-reported. Other data included were from the first entry in either HUNT2 or HUNT3, that is, the time of data collection when participants first reported having diabetes. Data were collected/measured at a median diabetes duration of 6.5 years in LADA and 5.4 years in type 2 diabetes.

All participants gave their informed consent. This project is approved by the Norwegian regional committee for medical and health research ethics.

2.2 | Selection of markers

We included markers that have been associated with the development of LADA or type 2 diabetes.[1,2] Sociodemographic markers were

gender and education (<14 or ≥14 years of education). Clinical markers were age at diagnosis (<50, 50-69 or ≥70 years), GADA level (high and low GADA grouped by median, 0.15ai), number of positive autoantibodies, obesity (body mass index [BMI] and waist circumference), thyroid disease (yes/no), HbA1c (<53 and ≥53 mmol/mol) and C-peptide levels (<0.3, 0.3-0.7 or >0.7 nmol/L). Markers of lifestyle were leisure-time physical activity (PA), smoking, alcohol frequency and coffee consumption. Individuals reporting light or hard PA at least once a week were categorized as moderate to high PA. Those reporting PA less than once a week were categorized into low/never PA. Smoking was categorized into current, former or never daily smoking, alcohol as less than once a week or once a week or more and coffee consumption as two or more, three to six, or seven or more cups per day. Genetic markers were T1D-GRS and type 2 diabetes associated genetic risk score (T2D-GRS) and first-degree family history of diabetes (FHD; yes/no).

2.3 | Genotyping and creation of genetic risk score

Genotyping was performed at the NTNU Genomic Core Facility at NTNU, Trondheim, Norway, using Illumina HumanCoreExome arrays (HumanCoreExom 12 v. 1.0, HumanCoreExome 12 v. 1.1 and HumanCoreExom 24 with custom content, Illumina, San Diego, CA). Imputation was performed using Minumac3 (v. 2.0.1) and a customized Haplotype Reference consortium release 1.1 (HRC v. 1.1).[16]

For T1D-GRS we selected 30 type 1 diabetes-associated single nucleotide polymorphisms (SNPs), a combination of human leukocyte antigen (HLA) and non-HLA SNPs.[17] Twenty-seven SNPs were directly available from the genotyping platform (Table S1). T1D-GRS calculation was not performed if genotyping results were missing for the greatest weighting HLA-DR3/DR4-DQ8 genotypes. For T2D-GRS we selected 178 SNPs that were reported as being associated with type 2 diabetes ($P = .5 \times 10^{-8}$) and identified in European ancestry.[18-21] Five SNPs were excluded because of failed QC (Table S2). Weighted T1D- and T2D-GRS were created by first multiplying the weight of each SNP with the number of risk alleles (0, 1, 2) for that SNP then summarizing the score over all SNPs. As weight we used the effect size (ln[OR]) for each SNP, as reported in the literature. Weights for DR3/DR4-DQ8 in the T1D-GRS were assigned based on imputed genotypes as described.[22] The GRSs were further categorized by the cut-off at median in low (≤median) and high (>median) T1D- and T2D-GRS.

TABLE 1 Participant characteristics by type of diabetes and insulin treatment within 10 years of diabetes debut

	LADA			Type 2 diabetes		
n	No insulin treatment 101	Insulin treatment 74	*P* value	No insulin treatment 2008	Insulin treatment 323	*P* value
Gender (male)	57 (56.4%)	35 (47.3%)	.232	1009 (50.2%)	175 (54.2%)	.190
Age at screening (y)	71.3 (63.0-77.7)	63.2 (53.4-70.5)	<.001	68.3 (59.0-75.4)	64.8 (55.6-71.8)	<.001
Age at diagnosis (y)	63 (57-70)	50 (44-60)	<.001	61 (52-68)	55 (47-62)	<.001
Duration of diabetes (y)	5.1 (2.4-11.0)	8.0 (5.1-13.7)	.005	5.1 (2.8-10)	8.9 (4.6-11.7)	<.001
Time to insulin initiation (y)		3.0 (2.0-5.0)			5.0 (2.0-7.0)	
BMI (kg/m^2)	27.7 (25.7-31.5)	27.3 (25.1-30.4)	.252	29.1 (26.4-32.5)	30.2 (27.4-34.2)	<.001
Waist circumference (cm)	97 (90-106)	92 (83-102)	.018	99 (91-107)	102 (93-110)	.001
Systolic blood pressure (mmHg)	150 (136-168)	141 (131-164)	.094	145 (131-163)	149 (133-163)	.449
Total cholesterol (mmol/L)	5.5 (4.7-6.5)	5.5 (4.7-6.6)	.764	5.6 (4.7-6.5)	5.7 (4.6-6.5)	.843
HDL cholesterol (mmol/L)	1.1 (0.9-1.4)	1.5 (1.1-1.8)	<.001	1.1 (1.0-1.4)	1.1 (0.9-1.3)	.002
Triglycerides (mmol/L)	2.10 (1.46-3.03)	1.26 (0.90-1.78)	<.001	2.04 (1.44-2.90)	2.20 (1.50-3.09)	.017
Glucose (non-fasting, mmol/L)	8.5 (6.5-12)	9.5 (6.8-14.2)	.035	7.9 (6.1-10.4)	10.3 (7.5-13.5)	<.001
HbA1c (mmol/mol)	56 (44-73)	70 (61-85)	<.001	55 (45-67)	67 (56-81)	<.001
HbA1c (%)	7.3 (6.2-8.8)	8.6 (7.7-9.9)	<.001	7.2 (6.3-8.3)	8.3 (7.3-9.6)	<.001
C-peptide (nmol/L)	0.89 (0.52-1.31)	0.20 (0.04-0.41)	<.001	0.88 (0.62-1.21)	0.52 (0.31-0.94)	<.001
GADA (ai)	0.11 (0.09-0.20)	0.72 (0.16-1.35)	<.001	NA	NA	
IA-2A (ai)	0.00 (0.00-0.02)	0.01 (0-0.04)	.005	NA	NA	
ZnT8A (ai)	0.01 (0.00-0.03)	0.01 (0-0.03)	.854	NA	NA	
T1D-GRS	6.8 (5.7-10.4)	10.7 (9.33-22.0)	<.001	6.7 (5.7-10.0)	6.7 (5.7-10.2)	.533
T2D-GRS	15.4 (15.1-15.9)	15.2 (14.8-15.8)	.071	15.6 (15.2-16.0)	15.6 (15.2-16.1)	.100

Note: The time point of data collection is from the first survey, HUNT2 or HUNT3, when participants reported having diabetes, which was at a median diabetes duration of 6.5 years in LADA and 5.4 years in type 2 diabetes. Data are shown as median (25-75 percentiles) or n (%).
Abbreviations: ai, antibody index; BMI, body mass index; GADA, glutamic acid decarboxylase autoantibodies; IA-2A, Islet antigen-2 autoantibodies; LADA, latent autoimmune diabetes in adults; T1D-GRS, type 1 diabetes genetic risk score; T2D-GRS, type 2 diabetes genetic risk score; ZnT8A, Zink transporter 8 autoantibodies.

TABLE 2 Differences in characteristics in participants who progressed to insulin dependency within 10 years subdivided by fast versus slow progressors by using median time to insulin initiation as cut-off

	LADA			Type 2 diabetes		
n	Insulin initiation >3 y after diagnosis 45	Insulin initiation ≤3 y after diagnosis 39	*P* value	Insulin initiation >5 y after diagnosis 125	Insulin initiation ≤5 y after diagnosis 198	*P* value
Gender (male)	10 (34.5%)	25 (55.6%)	.076	70 (56.0%)	105 (53.0%)	.602
Age at screening (y)	65. (55.9-69.4)	59.8 (53.3-70.8)	.435	65.9 (56.9-71.9)	64.2 (54.8-71.8)	.236
Age at diagnosis (y)	53 (44.5-60.5)	49 (42-59)	.468	56 (47.5-61)	54 (47-62)	.887
Duration of diabetes (y)	9.1 (5.4-13.3)	8 (4.0-14.6)	.517	10.2 (6.7-12.4)	6.9 (4.0-10.9)	<.001
BMI (kg/m^2)	27.8 (24.9-32.3)	26.8 (25.2-29.8)	.349	29.4 (27.1-34.0)	30.8 (27.9-34.6)	.093
Waist circumference (cm)	91 (87-102.5)	94 (80.5-102.5)	.769	99 (92-108)	103 (94-111)	.026
Systolic blood pressure (mmHg)	153 (132.5-170)	141 (131-155)	.131	153 (137-166)	143 (129-161)	.003
Total cholesterol (mmol/L)	5.6 (4.9-6.5)	5.3 (4.7-6.7)	.425	5.5 (4.6-6.4)	5.9 (4.7-6.5)	.469
HDL cholesterol (mmol/L)	1.3 (1.1-1.8)	1.5 (1.1-1.8)	.477	1.1 (0.9-1.3)	1.1 (0.9-1.3)	.315
Triglycerides (mmol/L)	1.32 (0.91-2.3)	1.17 (0.9-1.77)	.298	2.00 (1.47-2.81)	2.38 (1.57-3.32)	.059
Glucose (non-fasting, mmol/L))	12.2 (7.4-14.8)	9.3 (6.2-14.35)	.546	10.3 (7.6-13.6)	10.4 (7.5-13.5)	.918
HbA1c (mmol/mol)	69 (62-80)	70 (56-87)	.716	65 (58-81)	67 (56-80)	.905
HbA1c (%)	8.5 (7.8-9.5)	8.6 (7.3-10.1)	.716	8.1 (7.5-9.6)	8.3 (7.3-9.5)	.905
C-peptide (nmol/L)	0.33 (0.05-0.68)	0.07 (0.03-0.30)	.034	0.50 (0.30-0.81)	0.54 (0.31-0.99)	.278
GADA (ai)	0.32 (0.13-1.15)	1.05 (0.33-1.47)	.013	NA		
IA-2A (ai)	0.01 (0-0.03)	0.01 (0-0.05)	.673	NA		
ZnT8A (ai)	0 (0-0.03)	0.01 (0-0.04)	.539	NA		
Education ≥14 y of education	6 (20.7%)	15 (34.1%)	.216	14 (11.6%)	15 (8.1%)	.312
Age at diagnosis categorized			.865			.041
<50 y	13 (44.8%)	23 (51.1%)		36 (28.8%)	66 (33.3%)	
50-69 y	14 (48.3%)	19 (42.2%)		85 (68.0%)	113 (57.1%)	
≥70 y	2 (6.9%)	3 (6.7%)		4 (3.2%)	19 (9.6%)	
Number of Ab positive ≥2	4 (13.8%)	12 (26.7%)	.189	NA		
High GADA level (>median)	21 (72.4%)	38 (84.4%)	.209	NA		
High HbA1c (≥53 mmol/mol)	24 (96.0%)	32 (78.0%)	.048	97 (84.3%)	145 (81.9%)	.591
C-peptide categorization			.052			.319
<0.3 nmol/L	12 (48.0%)	25 (75.8%)		23 (24.2%)	38 (24.2%)	
0.3-0.7 nmol/L	7 (28.0%)	6 (16.2%)		42 (44.2%)	56 (35.7%)	
>0.7 nmol/L	6 (24.0%)	2 (6.1%)		30 (31.6%)	63 (40.1%)	
Thyroid disease (yes)	7 (24.1%)	11 (24.4%)	.976	14(11.3%)	33 (16.7%)	.184
Obesity, BMI > 30 (kg/m^2)	11 (37.9%)	10 (22.2%)	.143	55 (45.1%)	109 (56.2%)	.054
Waist circumference categorization[a]			.115			.052
Central lean	22 (48.9%)	11 (37.9%)		25 (20.2%)	30 (15.3%)	
Central overweight	3 (10.3%)	10 (22.2%)		30 (24.2%)	31 (15.8%)	

TABLE 2 (Continued)

	LADA			Type 2 diabetes		
n	Insulin initiation >3 y after diagnosis 45	Insulin initiation ≤3 y after diagnosis 39	*P* value	Insulin initiation >5 y after diagnosis 125	Insulin initiation ≤5 y after diagnosis 198	*P* value
Central obese	15 (51.7%)	13 (28.9%)		69 (55.6%)	135 (68.9%)	
Moderate to high physical activity	18 (81.8%)	34 (82.9%)	.912	85 (80.2%)	107 (66.0%)	.012
Alcohol frequency, once or more a week	6 (21.4%)	19 (46.3%)	.035	20 (17.4%)	30 (16.5%)	.839
Current daily smoker	3 (10.3%)	6 (13.6%)	.367	18 (14.8%)	36 (18 8%)	.529
Coffee consumption			.977			.634
≤2 cups a day	6 (21.4%)	10 (22.7%)		20 (16.4%)	39 (20.7%)	
3-6 cups a day	16 (57.1%)	24 (54.5%)		82 (67.2%)	120 (63.8%)	
≥7 cups a day	6 (21.4%)	10 (22.7%)		20 (16.4%)	29 (15.5%)	
First-degree family history of diabetes	17 (58.6%)	14 (33.3%)	.035	74 (61.2%)	105 (57.1%)	.478
High T1D-GRS (≥median)	15 (55.6%)	34 (82.9%)	.006	35 (29.2%)	63 (34.2%)	.355
High T2D-GRS (≥median)	10 (37.0%)	10 (24.4%)	.263	69 (57.5%)	92 (50%)	.200

Note: The time point of data collection is from the first survey, HUNT2 or HUNT3, when participants reported having diabetes, which was at a median diabetes duration of 6.5 years in LADA and 5.4 years in type 2 diabetes. Data are shown as median (25-75 percentiles) or n (%).

Abbreviations: Ab, autoantibody(ies); ai, antibody index; BMI, body mass index; GADA, glutamic acid decarboxylase autoantibodies; IA-2A, Islet antigen-2 autoanotbodies; LADA, latent autoimmune diabetes in adults; T1D-GRS, type 1 diabetes genetic risk score; T2D-GRS, type 2 diabetes genetic risk score; ZnT8A, Zink transporter 8 autoantibodies.

[a]Central lean, waist circumference ≤80 cm in females and ≤94 cm in males; central overweight, waist circumference 81-88 cm in females and 95-102 cm in males; central obesity, waist circumference >88 cm in females and >102 cm in males.

2.4 | Statistical analysis

Differences in clinical characteristics between the groups, (1) insulin treated versus non-insulin treated and (2) fast progressors versus slow progressors, based on cut-off by median time to insulin dependence in LADA and type 2 diabetes, were analysed by Mann–Whitney U test for continuous data and Pearson's χ^2 test for categorical data.

To identify possible predictors for insulin dependency, we first ran a Cox regression analysis adjusted for gender and age at diagnosis. Factors with a *P* value of less than .05 were considered as potential predictive factors and were further tested for being independent predictors for insulin dependency by running a multivariable Cox regression model with statistical adjustment for all the other potential factors. Genotyping batch and genetic principal components (PC1-4) were included in the model if a GRS was included. The proportional hazard assumption was checked visually (Kaplan–Meier plots) and by time-dependent covariate test for every factor included in the multivariable Cox regression model. If the Kaplan–Meier plots showed no intersections and the defined time-dependent covariate showed a *P* value of more than .05, we considered the proportional hazard assumption to be satisfied.

Patterns of missingness were evaluated both visually and by comparing participants with complete datasets included in the multivariable Cox regression with participants excluded because of missing information on at least one variable. All predictors included in the univariable Cox regression and the survival outcome variables (status and time to event) were included in the multiple imputation model. Five imputed datasets were created using 10 iterations. Cox regression was performed on each imputed dataset and a pooled value for the regression coefficient was automatically calculated.

Logistic regression and receiver operating characteristic (ROC) curve analysis were used to measure the discriminatory power of the possible predictive factors for insulin dependence.

All analyses were performed using IBM SPSS Statistics 25.

3 | RESULTS

We identified 175 LADA and 2331 type 2 diabetes participants from the HUNT2 and HUNT3 cohorts. Among these, 42% with LADA and 14% with type 2 diabetes reported that they had started insulin treatment within 10 years, with a median time to insulin initiation of 3 years for LADA and 5 years for type 2 diabetes. The characteristics of LADA and type 2 diabetes participants by insulin treatment are shown in Table 1. Both LADA and type 2 diabetes participants who started insulin treatment within 10 years were younger when

TABLE 3 Hazard ratios (HRs) for time to insulin dependence censored at 10 years after diabetes diagnosis in LADA and type 2 diabetes, and the proportion of insulin treated within 10 years for each category

	LADA					Type 2 diabetes				
	Proportion (% [95% CI]) insulin treated within 10 y	Univariable analysis		Multivariable analysis		Proportion (% [95% CI]) insulin treated within 10 y	Univariable analysis		Multivariable analysis	
		HR [95% CI]	*P* value	HR [95% CI]	*P* value		HR [95% CI]	*P* value	HR [95% CI]	*P* value
Gender										
Male	47.0 [36.3-57.7]	Ref		Ref		12.9 [11.0-14.8]	Ref		Ref	
Female	38.0 [28.1-48.0]	1.38 [0.87-2.18]	.174	1.09 [0.52-2.31]	.816	14.8 [12.8-16.8]	0.88 [0.70-1.09]	.237	0.77 [0.59-1.01]	.062
Education										
<14 y of school	37.4 [29.4-45.5]	Ref		Ref		14.4 [12.8-16.0]	Ref			
≥14 y of school	72.4 [56.1-88.7]	2.01 [1.17-3.45]	.011	0.52 [0.21-1.27]	.151	11.9 [7.9-16.0]	0.77 [0.52-1.13]	.184		
Age at diagnosis, y										
<50	81.8 [70.4-93.2]	5.73 [2.24-14.6]	<.001	1.54 [0.32-7.30]	.588	21.8 [18.1-25.5]	3.17 [2.01-4.99]	<.001	2.83 [1.56-5.15]	.001
50-69	34.0 [24.6-43.4]	1.78 [0.69-4.57]	.23	0.67 [0.17-2.71]	.577	14.3 [12.5-16.2]	2.16 [1.40-3.34]	<.001	2.11 [1.19-3.74]	.01
≥70	14.7 [2.8-26.6]	Ref		Ref		4.8 [2.9-6.7]	Ref		Ref	
Number of Ab-pos										
1 ab	37.4 [29.8-45.0]	Ref		Ref			NA			
≥2 ab	80.0 [62.5-97.5]	3.38 [1.87-6.12]	<.001	3.66 [1.32-10.1]	.012					
GADA level (ai)										
Low (<median)	17.0 [9.2-24.9]	Ref		Ref			NA			
High (≥median)	67.8 [58.0-77.6]	4.75 [2.55-8.85]	<.001	2.67 [1.04-6.85]	.041					
HbA1c										
<53 mmol/mol (7.0%)	21.3 [9.6-33.0]	Ref				6.6 [4.8-8.4]	Ref			
≥53 mmol/mol (7.0%)	50.9 [41.6-60.3]	1.70 [0.86-3.39]	.129			21.3 [18.9-23.7]	2.77 [2.04-3.76]	<.001	2.44 [1.72-3.46]	<.001
C-peptide										
<0.3 nmol/L	86.0 [75.7-96.4]	6.47 [2.83-14.83]	<.001	6.40 [2.02-20.3]	.002	46.6 [38-55.1]	4.33 [3.13-5.99]	<.001	5.01 [3.53-7.10]	<.001
0.3-0.7 nmol/L	31.7 [17.5-46.0]	2.17 [0.89-5.28]	.089	2.21 [0.72-6.84]	.168	19.6 [16.1-23]	1.94 [1.46-2.58]	<.001	2.40 [1.78-3.24]	<.001
>0.7 nmol/L	12.5 [4.4-20.6]	Ref		Ref		8.7 [7.0-10.3]	Ref		Ref	

TABLE 3 (Continued)

	LADA					Type 2 diabetes				
	Proportion (% [95% CI]) insulin treated within 10 y	Univariable analysis		Multivariable analysis		Proportion (% [95% CI]) insulin treated within 10 y	Univariable analysis		Multivariable analysis	
		HR [95% CI]	*P* value	HR [95% CI]	*P* value		HR [95% CI]	*P* value	HR [95% CI]	*P* value
Waist circumference[a]										
Central lean	57.9 [45.1-70.7]	1.96 [1.16-3.32]	.012	0.57 [0.24-1.35]	.569	13.4 [10.1-16.7]	Ref		Ref	
Central overweight	29.5 [16.1-43.0]	1.03 [0.51-2.07]	.928	0.84 [0.30-2.35]	.842	11.4 [8.7-14.1]	0.95 [0.66-1.36]	.763	1.35 [0.88-2.07]	.167
Central obese	38.9 [27.6-50.1]	Ref		Ref		15.0 [13.1-16.9]	1.47 [1.08-0.93]	.015	1.65 [1.06-2.55]	.026
BMI (kg/m^2)										
<30 Normal/overweight	45.3 [36.3-54.3]	Ref				11.6 [9.9-13.4]	Ref		Ref	
≥30 Obese	38.2 [25.3-51.0]	0.72 [0.43-1.21]	.214			16.6 [14.3-19.0]	1.56 [1.25-1.96]	<.001	1.73 [1.23-2.41]	.001
Alcohol frequency										
Less than once/wk	35.2 [26.8-43.6]	Ref		Ref		14.1 [12.4-15.7]	Ref			
Once or more/wk	64.1 [49.0-79.2]	2.65 [1.53-4.59]	.001	1.63 [0.70-3.76]	.254	12.8 [9.5-16.1]	0.88 [0.64-1.20]	.419		
T1D-GRS										
Low (median)	23.1 [13.7-32.4]	Ref		Ref		13.5 [11.8-15.2]	Ref			
High (median)	64.9 [54.3-75.6]	3.66 [2.04-6.58]	<.001	1.64 [0.73-3.68]	.228	15.4 [12.6-18.2]	1.11 [0.88-1.42]	.38		

Abbreviations: Ab, autoantibody(ies); Ab-pos, autoantibody(ies) positive; ai, antibody index; BMI, body mass index; GADA, glutamic acid decarboxylase autoantibodies; LADA, latent autoimmune diabetes in adults; T1D-GRS, type 1 diabetes genetic risk score.

[a]Central lean, waist circumference ≤80 cm in females and ≤94 cm in males; central overweight, waist circumference 81-88 cm in females and 95-102 cm in males; central obesity, waist circumference >88 cm in females and >102 cm in males.

diagnosed, had higher blood glucose and HbA1c levels and lower C-peptide levels compared with participants who had not started with insulin. GADA levels and T1D-GRS were higher in LADA participants who started with insulin compared with those who did not, whereas BMI was higher in insulin starters in the type 2 diabetes category.

We compared fast versus slow progressors by using median time to insulin initiation as cut-off (Table 2). Participants with LADA who progressed faster to insulin dependency (within 3 years after diagnosis) had a higher GADA level ($P = .013$), lower C-peptide levels ($P = .034$) and higher T1D-GRS ($P = .006$) compared with slow progressors. Fast progressors were less probable to have a first-degree FHD ($P = .035$), more probable to drink alcohol at least once a week ($P = .035$) and were less probable to have HbA1c values of 53 mmol/mol or higher ($P = .048$). Type 2 diabetes fast progressors (defined as insulin initiation within 5 years after diagnosis) had a shorter duration of diabetes ($P < .001$), higher waist circumference ($P = .026$) and were less physically active ($P = .012$) compared with slow progressors.

3.1 | Identifying possible predictors of insulin dependency

Univariable Cox regression analyses indicated that younger age at diagnosis was a possible predictive factor for insulin dependency for LADA and

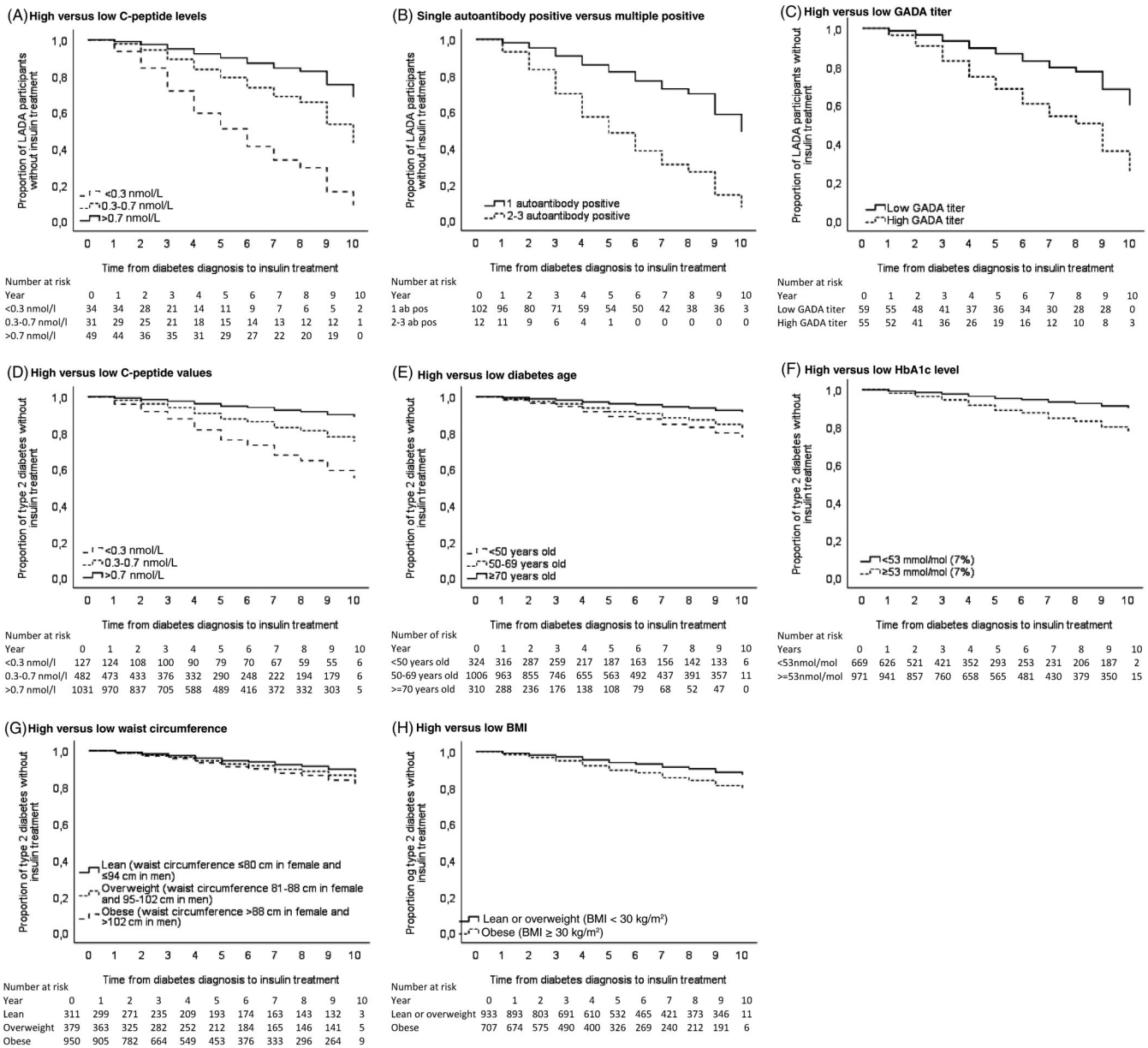

FIGURE 1 Kaplan–Meier curves showing the associations of (A) C-peptide, (B) number of autoantibodies (ab pos) and (C) high and low glutamic acid decarboxylase autoantibodies (GADA) levels for the development of insulin dependence within 10 years after diabetes diagnosis in participants with latent autoimmune diabetes in adults (LADA), and the association of (D) high and low C-peptide, (E) age at diagnosis, (F) high and low HbA1c and obesity, based on (G) waist circumference and (H) body mass index (BMI), with the development of insulin dependence within 10 years after diabetes diagnosis in participants with type 2 diabetes

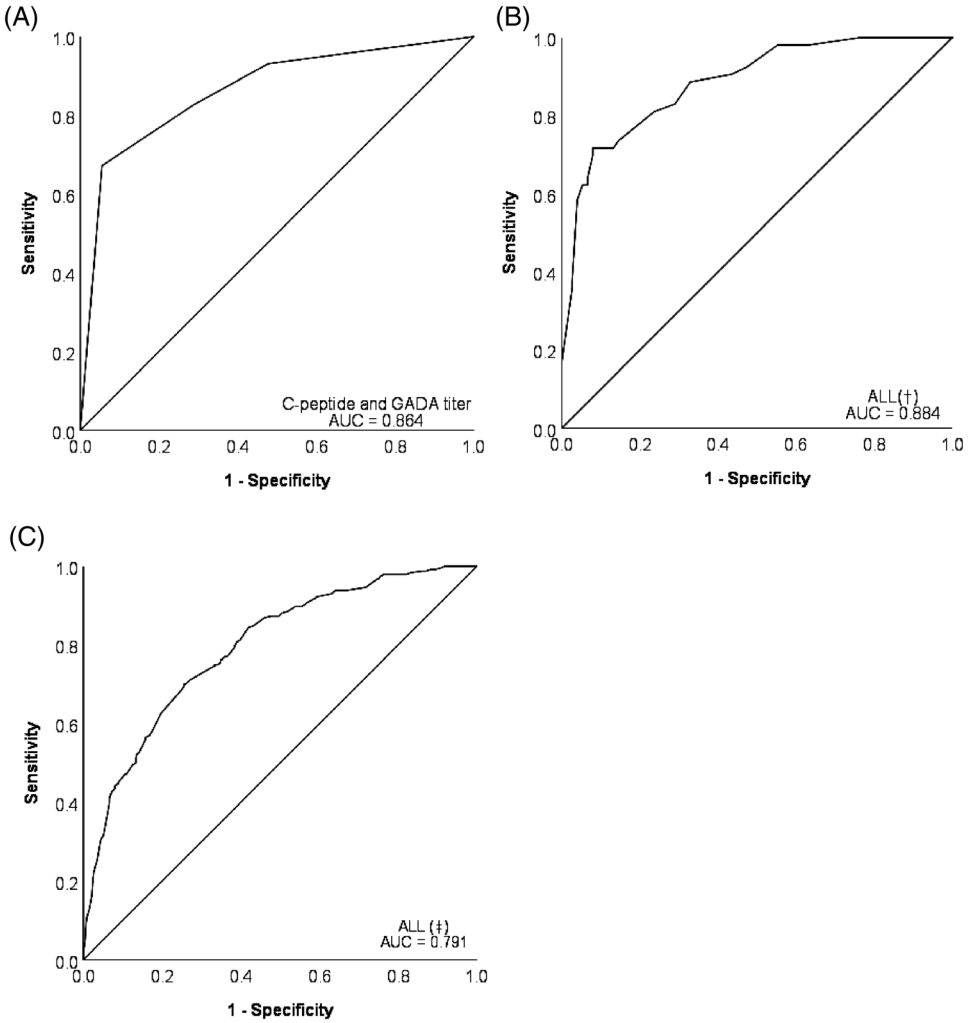

FIGURE 2 Receiver operating characteristic curve analysis showing the strongest predictors of insulin dependency in LADA; (A) C-peptide and glutamic acid decarboxylase autoantibodies (GADA) level; (B) †GADA level, C-peptide, number of positive autoantibodies, gender and type 1 diabetes genetic risk score (T1D-GRS) and in type 2 diabetes in combination; (C) ‡Age at diagnosis, HbA1c, C-peptide, central overweight/obesity (waist circumference) and obesity (body mass index). AUC, area under the curve

type 2 diabetes ($P < .001$ for both), as were low C-peptide values (<0.3 nmol/L; $P < .001$ for both; Table 2). Being central lean (waist circumference <80 cm in females and <94 cm in males; $P = .012$) was a possible predictor for LADA. This was in marked contrast to participants with type 2 diabetes, in whom being obese, both centrally (waist circumference >88 cm in females and >102 cm in males; $P = .015$) and by BMI (>30 kg/m^2; $P < .001$), were possible predicting factors for progression. Exclusive predicting factors for insulin dependency in LADA were high levels of GADA ($P < .001$), multiple autoantibody positivity ($P < .001$), having a high T1D-GRS ($P < .001$), higher alcohol consumption ($P < .001$) and a higher level of education ($P < .001$). High HbA1c values ($P < .001$) was a possible predictive factor only in type 2 diabetes.

Neither in LADA nor in type 2 diabetes were PA, smoking, coffee consumption, FHD and T2D-GRS predicting factors for insulin dependency (Table S3).

3.2 | Independent predictors for progression to insulin dependence

Factors found in the univariable models with P less than .05 were included in a multivariable Cox regression analysis, as was gender. The multivariable analysis was first performed on 114 LADA and 1640 type 2 diabetes patients for whom complete data were available. Low fasting levels of C-peptide was an independent predictor for progression to insulin dependency both in LADA and type 2 diabetes (<0.3 nmol/L; HR 6.40 [95% CI, 2.02-20.3] in LADA and HR 5.01 [95% CI, 3.53-7.10] in type 2 diabetes; Table 3). Having high levels of GADA was an independent predictor for progression in LADA (HR 5.37 [95% CI, 1.17-24.6]), as was multiple autoantibody positivity (HR 3.66 [95% CI, 1.32-10.1]). Corresponding Kaplan–Mayer curves for LADA are shown in Figure 1.

In type 2 diabetes (Table 3), younger age at diagnosis (<50 years: HR 2.83 [95% CI, 1.56-5.15]; 50-69 years: HR 2.11 [95% CI, 1.19-3.74]), high levels of HbA1c (≥53 mmol/mol; HR 2.44 [95% CI, 1.72-3.46]), central obesity (HR 1.65 [95% CI, 1.06-2.55]) and a BMI of more than 30 kg/m^2 (HR 1.73 [95% CI, 1.23-2.41]) were independent predictors. Kaplan–Mayer curves are shown in Figure 1.

There were no significant differences between the clinical characteristics of non-missing and missing groups in LADA. For type 2 diabetes there were minor differences (Table S4).

After multiple imputation the significant predictors for insulin dependence in univariable analysis among LADA participants were similar to those in the complete case analysis (data not shown). Low

C-peptide and high GADA level were still significant after pooling the imputed datasets in a multivariable Cox regression, and two new predictors, female gender (pooled HR 1.80 [95% CI, 1.02-3.19]) and high T1D-GRS (pooled HR 2.23 [95% CI, 1.13-4.39]), became significant (Table S5).

Multiple imputation in type 2 diabetes yielded similar results for univariable analysis as for the complete case analysis. In contrast to LADA, male rather than female (HR 1.30 [95% CI, 1.02-1.65]) became a significant predictor after pooling the imputed datasets (Table S5).

3.3 | ROC curves

High GADA level and low C-peptide values were each fairly discriminatory between non-progressors and progressors in LADA (area under the curve [AUC] 0.76 [95% CI, 0.69-0.83] and 0.83 [95% CI, 0.76-0.91], respectively). When combined, the discriminatory power increased to an AUC of 0.86 [95% CI, 0.80-0.93] (Figure 2A). Adding multiple autoantibody positivity, T1D-GRS and gender only marginally increased the discriminator power, AUC, from 0.86 to 0.88 (Figure 2B).

The criteria of having C-peptide values less than 0.3 nmol/L and a high GADA level (>0.15ai)—20% of the participants with LADA satisfied that criteria—had 98.9% (95% CI, 93.9%-100%) specificity and 45.5% sensitivity (95% CI, 33.1%-58.2%) for identifying LADA patients with progression to insulin dependence within 10 years, with a positive predictive value of 96.8% (95% CI, 80.8%-99.5%) and a negative predictive value of 71.0% (95% CI, 66.2%-75.3%).

In type 2 diabetes, the predictive factors reached a moderately discriminatory power only in combination (AUC 0.79 [95% CI, 0.76-0.82]; Figure 2C). Adding gender to the model did not change the discriminatory power (AUC 0.791 to 0.794). The criteria of having C-peptide values of less than 0.7 nmoL/L, age at diagnosis of younger than 70 years, HbA1c of 53 mmol/mol or higher and being obese, either centrally or by BMI, had 95% specificity (95% CI, 94%-96%) and 29% sensitivity (95% CI, 23%-34%) for identifying type 2 diabetes patients with progression to insulin dependence within 10 years, with a positive predictive value of 48% (95% CI, 42%-55%) and a negative predictive value of 89% (95% CI, 89%-90%).

4 | DISCUSSION

Our study shows, in an all-population–based cohort, both similarities as well as differences between LADA and type 2 diabetes for factors that predict progression to insulin dependency. Regarding similarities, a low C-peptide level (<0.3 nmol/L in LADA and <0.7 nmol/L in type 2 diabetes) was a strong independent predictor in both LADA and type 2 diabetes. Regarding differences, a high GADA level was an independent predictor in LADA, whereas a younger age at diagnosis, high HbA1c values and obesity were independent predictors only in type 2 diabetes.

Lower C-peptide values in insulin treated versus not insulin treated in HUNT have been reported previously.[6] However, to our knowledge, this is the first study to show a shared association between low C-peptide levels in LADA and type 2 diabetes. This does not imply that the same aetiological factors are operative. A possible cause of progression to insulin treatment in our type 2 diabetes participants could be chronic beta-cell stress as a result of insulin resistance. In this context it appears that our insulin-prone type 2 diabetes patients do not fit the category of a severely insulin-deficient subgroup of type 2 diabetes without signs of autoimmunity, as defined by Ahlqvist et al.,[23] as the type 2 diabetes subgroup of Ahlquist et al. is associated with low BMI, which is in contrast to our patients.

A recent consensus statement from an international expert panel forwarded recommendations for insulin treatment in LADA based on C-peptide levels.[24] However, our results show that a constellation of C-peptide and levels of GADA gives higher precision than C-peptide alone. A recent Chinese study investigating the time dynamics of beta-cell failure, as measured by decline in fasting C-peptide, emphasizes this constellation by showing that a high GADA titer was the strongest predictive factor for beta-cell failure.[25]

An association between progression to insulin dependence in LADA and high levels of GADA is in line with previous studies, although they may differ to some extent.[5,8] Thus, numbers of autoantibodies and not GADA levels were reported as an independent predictor for insulin dependency.[9,10] Another study found that high GADA levels and not the presence of multiple autoantibodies were significant predictors.[8] Our data agree with a review that concludes that both GADA levels and/or multiple autoantibody positivity can predict beta-cell failure in LADA.[26] Additionally, we show here a graded effect of GADA levels on the time to insulin dependence (Table 2).

Levels of HbA1c were a marker for progression in type 2 diabetes but not in LADA, thus presenting an apparent paradox. In type 1 diabetes, in a short space of time, almost normal glucose control can develop into profound hyperglycaemia, presumably because all compensatory measures of glucose control have been exhausted in an accelerated fashion.[27] By analogy, a similar mechanism may be operative in LADA. Deterioration of glucose control in type 2 diabetes appears to follow a more protracted course,[28] influenced by a slower decline than in LADA.

A high T1D-GRS was reported to be a strong independent predictive factor for rapid progression to insulin dependence in LADA.[5] However, adding the T1D-GRS to the ROC analysis in our study did not considerably increase the discriminatory power between non-progressors and progressors to insulin dependence. From an aetiological point of view, it can be envisaged that low C-peptide is a result of autoimmune assault, which is in turn partly attributable to genetic causes.

Grubb et al. suggest that a T1D-GRS could be used together with GADA to predict progression to insulin dependence.[5] However, genetic tests are currently not easily accessible in the clinic.[29] Our finding, that LADA patients with a constellation of C-peptide levels of less than 0.3 nmol/L and high GADA levels will probably progress to

insulin dependence, would appear to provide sufficient and easily obtainable data for the clinician to assess the prognosis for a future insulin dependency in a significant number of LADA patients. Factors that lend discriminating power in type 2 diabetes had less impact, perhaps because still unknown factors are important for progression in type 2 diabetes.

We found that a T2D-GRS did not predict progression in type 2 diabetes, a finding which is in line with a report from a European cohort.[30] Genetics for type 2 diabetes are mostly associated with effects on beta cells and not to a major extent with insulin resistance. Our findings on T2D-GRS thus support the notion that insulin resistance and its non-genetic causes are major factors behind progression to insulin treatment in type 2 diabetes. Prolonged insulin resistance is known to induce beta-cell stress and could result in beta-cell deterioration, highlighted in obese paediatric patients[31] and measurable by low levels of C-peptide, as found here.

Our findings on gender are noteworthy. Gender emerged as a predictive factor in the enlarged analysis, which included imputed cases. Interestingly, the gender effect was opposite in LADA and type 2 diabetes, female gender being a predictor in LADA, whereas male gender was a predictor in type 2 diabetes. Some evidence supports the finding in LADA, as higher levels of GADA have been reported for females with LADA,[32] indicating a higher level of autoimmunity. Regarding type 2 diabetes, there appears to be no consensus in epidemiological studies as to a gender effect.

A strength of this study is the inclusion of a cohort that is phenotypically well characterized and based on all-population surveys. One possible limitation is that the choice of treatment was determined by the participants' general practitioner, rather than by adherence to a clinical protocol. However, clinical guidelines for treatment of different forms of diabetes have been uniform for decades in Norway. The question arises as to what extent measurements of autoantibodies, primarily GADA, were in use during the years encompassing the current study. Available evidence, albeit largely anecdotal, indicates that autoantibodies were rarely measured in adult-onset diabetes patients who did not clinically require insulin. However, given uncertainties on this point, it should not affect a comparison within the category of LADA or type 2 diabetes concerning progression to insulin dependence. As to further limitations, data on insulin treatment and calculation of time to insulin initiation were based on self-reported values and therefore subject to some degree of uncertainty. For some of the participants we could confirm such data by registering identical answers at two visits (HUNT2 and HUNT3); however, for most of the participants, we only had access to data from a single visit. Lastly, a replication cohort for confirmation of the results would have strengthened the study.

In conclusion, low C-peptide values in conjunction with high GADA levels predict progression to insulin dependency in LADA. The predictive ability of these factors in LADA was greater than for a combination of multiple factors in type 2 diabetes. These findings should be of practical value for clinicians treating LADA patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

VG and EPS designed the study. EPS was responsible for drafting of the manuscript and analyzing the data and takes full responsibility for the accuracy of the analyses. All authors contributed to the interpretation of the results and critically revised and approved the final version of the manuscript.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data are available up on request to HUNT Research Center (hunt.no, kontakt@hunt.ntnu.no)

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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