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Clinical utility of novel diabetes subgroups in predicting vascular complications and mortality: up to 25 years of follow-up of the HUNT Study

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ABSTRACT

Introduction Cluster analysis has previously revealed five reproducible subgroups of diabetes, differing in risks of diabetic complications. We aimed to examine the clusters' predictive ability for vascular complications as compared with established risk factors in a general adult diabetes population.

Research design and methods Participants from the second (HUNT2, 1995–1997) and third (HUNT3, 2006–2008) surveys of the Norwegian population-based Trøndelag Health Study (HUNT Study) with adult-onset diabetes were included (n=1899). To identify diabetes subgroups, we used the same variables (age at diagnosis, body mass index, HbA1c, homeostasis model assessment estimates of beta cell function and insulin resistance, and glutamic acid decarboxylase antibodies) and the same data-driven clustering technique as in previous studies. We used Cox proportional hazards models to investigate associations between clusters and risks of vascular complications and mortality. We estimated the C-index and R^2 to compare predictive abilities of the clusters to those of established risk factors as continuous variables. All models included adjustment for age, sex, diabetes duration and time of inclusion.

Results We reproduced five subgroups with similar key characteristics as identified in previous studies. During median follow-up of 9–13 years (differing between outcomes), the clusters were associated with different risks of vascular complications and all-cause mortality. However, in prediction models, individual established risk factors were at least as good predictors as cluster assignment for all outcomes. For example, for retinopathy, the C-index for the model including clusters (0.65 (95% CI 0.63 to 0.68)) was similar to that of HbA1c (0.65 (95% CI 0.63 to 0.68)) or fasting C-peptide (0.66 (95% CI 0.63 to 0.68)) alone. For chronic kidney disease, the C-index for clusters (0.74 (95% CI 0.72 to 0.76)) was similar to that of triglyceride/high-density lipoprotein ratio (0.74 (95% CI 0.71 to 0.76)) or fasting C-peptide (0.74 (95% CI 0.72 to 0.76)), and baseline estimated glomerular filtration rate yielded a C-index of 0.76 (95% CI 0.74 to 0.78).

Conclusions Cluster assignment did not provide better prediction of vascular complications or all-cause mortality compared with established risk factors.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Researchers have proposed five new subgroups of diabetes found through k-means clustering that are reproducible across diabetes cohorts and associated with different risks of vascular complications.

⇒ It has been envisioned that these subgroups could be implemented in clinical practice, with one of the aims being to improve personalized prediction of complications.

WHAT THIS STUDY ADDS

⇒ We confirmed increased risks of complications for the severe subgroups, but most of these disappeared when adjusting for HbA1c or cardiovascular risk factors.

⇒ In prediction models, individual established risk factors were at least as good predictors as subgroup allocation for all outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ In a general diabetes population, the predictive ability of diabetes subgroups does not appear to be sufficient for these to be useful for implementation in clinical practice for the purpose of personalized prediction and prevention of complications.

INTRODUCTION

The pathogenesis of type 2 diabetes involves a complex interplay between genetic and environmental factors resulting in insulin resistance and beta cell dysfunction. The contributions of each factor differ between patients, leading to different clinical presentations of diabetes with varying disease

progression and risks of vascular complications. In recent years, attempts have been made to detangle this heterogeneity.[1–4] In 2018, Ahlqvist *et al* proposed five subgroups of diabetes identified through data-driven cluster analysis of six clinical variables acquired shortly after diabetes diagnosis in the All New Diabetics in Scania (ANDIS) cohort: age at diagnosis, body mass index (BMI), HbA1c and homeostasis model assessment of beta cell function (HOMA2-B) and insulin resistance (HOMA2-IR), and glutamic acid decarboxylase (GAD) antibodies.[1] Several studies have replicated this technique and demonstrated that similar subgroups may be found in a range of diabetes cohorts.[5–8] The subgroups display different risks of vascular complications, with higher risk of retinopathy and neuropathy in the severe insulin-deficient diabetes (SIDD) subgroup,[1 5 8] higher risk of chronic kidney disease in the severe insulin-resistant diabetes (SIRD) subgroup,[1 5 6 8 9] and lower risks of complications in the mild obesity-related diabetes (MOD) subgroup and the mild age-related diabetes (MARD) subgroup. Although the original study mainly focused on populations of newly diagnosed diabetes, they found similar clusters in a cohort of participants with longer durations of diabetes, and suggested that the subgroups could be stable over time.[1] It has been postulated that these subgroups could be implemented in clinical practice for a personalized medicine approach where the intensity of preventive medication and follow-up could be directed by the individual's assigned subgroup.[10 11] However, the utility of clusters in predicting complications is unclear. A study by Dennis *et al* found estimated glomerular filtration rate (eGFR) as a continuous variable to be better at predicting chronic kidney disease and age at diagnosis to be better at predicting glycemic progression than subgroup designation,[6] but this study was performed in a highly selected randomized controlled trial (RCT) population with up to 5 years of follow-up. Thus, in a population-based study with up to 25 years of follow-up, we aimed to investigate the subgroups' prognostic utility for vascular complications, compared with that of established risk factors. We conducted our study in a population of varying diabetes duration, mimicking the clinical scenario where clusters would be used for prediction of complications in a general adult diabetes population.

METHODS

Study population

The Trøndelag Health Study (HUNT Study) includes four comprehensive population-based surveys (HUNT1–HUNT4) conducted in the Nord-Trøndelag region of Norway. At 11-year intervals during 1984–2019, all inhabitants ≥20 years in Nord-Trøndelag were invited to participate in surveys, including questionnaires, clinical examinations and in HUNT2–4, blood sampling.[12] The current study included participants with self-reported diabetes in HUNT2 (1995–1997) or HUNT3 (2006–2008), who were invited to participate in supplemental diabetes-specific studies. In HUNT2, 2028 participants (3.1%) had self-reported diabetes, and 1481 (73%) of them participated in the diabetes study. In HUNT3, 2264 participants (4.5%) had self-reported diabetes, and 1252 (55%) participated in the diabetes study. Among them, 1899 individuals with adult-onset diabetes (onset at ≥20 years) and sufficient information for cluster designation were included in the study (online supplemental figure 1). In those who participated in both surveys and had no missing variables in either survey (n=143), variables from HUNT2 were used.

To achieve information on outcomes, survey data from HUNT2 and HUNT3 were linked to national and regional health registers using the unique 11-digit national identity number assigned to all Norwegian residents. Linkage was made to prospectively recorded International Classification of Diseases-9 (ICD-9) and ICD-10 codes from the patient administrative systems at the hospitals in the Central Norway region, including all ICD codes registered at day-clinic visits and hospital admissions from September 1987 to December 2020, and all creatinine measurements performed at the laboratories of those hospitals from December 1992 to December 2020. Furthermore, linkage was made to ICD codes from private practicing specialists from the Norwegian Control and Payment of Health Reimbursements Database (from January 2006 to December 2020); ICD-10 codes from all Norwegian hospitals, from the Norwegian Patient Registry (from January 2008 to December 2020); and to the Norwegian Cause of Death Registry comprising information on time and cause of death for all citizens.

Data collection and laboratory measurements

In each survey, questionnaires included information on age at diabetes diagnosis, family history of diabetes, history of cardiovascular disease (CVD) and diabetic complications, and use of glucose-lowering and antihypertensive medications. Height, weight, and waist and hip circumference were measured by specially trained health personnel, and BMI (weight in kilograms divided by the squared value of height in meters) calculated. Blood pressure was measured three times, and we used the mean value of the second and third measurements, or either the second or third if one of them was missing. Glucose and C-peptide levels were measured in serum samples after an overnight fast. C-peptide was analyzed by radioimmunoassay (RIA, Diagnostic Systems Laboratories, Texas, USA) in HUNT2, and by immunofluorometric assay in HUNT3. HOMA estimates of beta cell function (HOMA2-B) and insulin resistance (HOMA2-IR) were calculated based on fasting C-peptide and glucose using the University of Oxford calculator.[13] In participants where fasting serum glucose was missing, glucose measured in capillary full blood and transformed to plasma values was used (n=169). GAD antibodies were measured in serum samples and analyzed by immunoprecipitation radioligand assay using translation labeled 3H-GAD65 as a labeled reagent (Novo Nordisk, Bagsværd,

Denmark). GAD antibody levels were expressed as an antibody index (ai) relative to a standard serum, and elevated GAD antibodies were defined as ai≥0.08.[14] HbA1c was measured in whole blood samples and analyzed based on high-performance liquid chromatography with equipment from Shimadzu in HUNT2, and by using an accredited enzymatic method from Abbott in HUNT3 (Reagent kit; 02K96-20 (0142473E) Hemoglobin A1c (Multigent, Abbott Laboratories, USA)). Total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, C reactive protein, alanine aminotransferase and creatinine were measured in non-fasting serum samples. We calculated the triglyceride/HDL ratio by dividing triglyceride level (mmol/L) by HDL cholesterol level (mmol/L). We estimated low-density lipoprotein (LDL) cholesterol levels using the Sampson equation,[15] and the glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration equation.[16]

Definitions of vascular complications

Myocardial infarction was defined by ICD-10 code I21 and ICD-9 code 410 from hospital records or from the Norwegian Cause of Death Registry. Stroke was defined by ICD-10 codes I60–I61 and I63–I64, and ICD-9 codes 430–431 and 434 from hospital records or from the Norwegian Cause of Death Registry. Retinopathy was defined by ICD-10 codes H36.0 and E10.3–14.3, and ICD-9 codes 362.0 and 250.5. Chronic kidney disease stage 3 and higher was defined as having three measurements of eGFR<60 mL/min/1.73 m^2 at three separate time points in laboratory data from the Central Norway public hospitals (measurements recorded within the same month were excluded to avoid including patients with acute rather than chronic kidney disease). Chronic kidney disease stage 4 and higher was defined as having three measurements of eGFR<30 mL/min/1.73 m^2 at three separate time points from laboratory data.

Statistical analysis

The cluster analysis was performed as in the study by Ahlqvist *et al*.[1] First, participants with elevated GAD antibodies were assigned to the severe autoimmune diabetes (SAID) subgroup and were not included in the cluster analysis; this subgroup represents type 1 diabetes and latent autoimmune diabetes in adults in the traditional classification of diabetes. For the remaining participants, we standardized all cluster variables (age at diagnosis, BMI, HbA1c, HOMA2-B and HOMA2-IR) to a mean of 0 and SD of 1 separately for men and women. Participants with one or more extremely outlying variables (z>5 SD) were excluded (n=10). We used the elbow method, the gap statistic, and the mean silhouette width to assess the optimal number of clusters in our data.[17–19] We did not find evidence of a clear optimal number of clusters (online supplemental figure 2), and thus instructed the cluster analysis to form four clusters, as has been done in previous studies. We performed a k-means cluster analysis using the kmeansruns command in the fpc package in R. Since we had a smaller sample size than the study by Ahlqvist *et al*, we chose not to perform separate cluster analyses for men and women. To evaluate the stability of clusters we estimated the Jaccard coefficient.[20]

In addition to grouping our participants according to our 'de novo' cluster analysis, as described above, in sensitivity analyses we used two alternative strategies to form clusters: First, to investigate whether clusters formed based on variables close to the time of diagnosis would give better prediction, we performed a similar cluster analysis restricted to participants with short diabetes duration (<3 years, n=502). Second, to investigate whether predefined clusters from the Ahlqvist study performed better than the clusters formed in our cluster analysis, we grouped our participants based on their nearest cluster centers ('centroids') from ANDIS coordinates. Finally, to investigate the stability of clusters over time, we performed an additional analysis where we used measurements from HUNT3 instead of HUNT2 in those who had participated in both surveys.

To investigate differences in risk of complications across up to 25 years of follow-up, we performed Cox proportional hazards models to estimate HRs between subgroups, adjusting for age, sex, diabetes duration, and time of inclusion (HUNT2 or HUNT3). We used time in study as the timescale. The proportional hazards assumption was assessed by visual inspection of log-minus-log plots and tested using Schoenfeld residuals. Participants with known previous events were excluded, including those with self-report of a previous event. For the analyses of incident chronic kidney disease stage 3 or 4, we excluded those with an eGFR<60 mL/min/1.73 m^2 or <30 mL/min/1.73 m^2 at the HUNT examination, respectively. Follow-up started on the date of HUNT participation and ended on December 31, 2020. To investigate if differences in hazard were mediated by differences in HbA1c between subgroups, we additionally adjusted for baseline HbA1c. In a third model, we made additional adjustments for commonly measured cardiovascular risk factors (BMI, waist circumference, systolic and diastolic blood pressure, eGFR, LDL cholesterol, and triglyceride/HDL cholesterol ratio). To investigate differences between subgroups in the prevalence of diabetic and cardiovascular complications acquired before HUNT participation, we used log-binominal regression to estimate prevalence ratios.

To compare the predictive ability of clusters to that of established risk factors, we estimated the Harrell's concordance index (C-index with CIs),[21] and Royston and Sauerbrei's R^2 statistic,[22] adjusted for the number of covariates, for different Cox proportional hazards models. We included adjustments for age, sex, diabetes duration, and time of inclusion (HUNT2 or HUNT3) in every model. As a sensitivity analysis, the same analyses were repeated in the subset of participants with short duration of diabetes (<3 years since diagnosis). For the purpose of comparison, we also investigated the predictive ability of phenotype-based subgroups of diabetes

suggested by Stidsen *et al*,[3] defined by HOMA2-B and HOMA2-IR measurements, using cut-off values from the original study. Since the cut-off values were difficult to extrapolate to longer duration diabetes, we only investigated these subgroups in the short duration group. Finally, to compare differences in cluster variables between those with short or long duration of diabetes, we used analysis of variance.

The cluster analyses were performed using R V.4.3.2 (CRAN, https://cran.r-project.org/). Other analyses were performed using Stata software (StataCorp. 2019. Stata Statistical Software: Release 17. College Station, Texas: StataCorp).

RESULTS

The 1899 participants had a mean age at baseline of 65.6 years (SD 11.9), and 49% of participants were women (table 1). Median duration of diabetes was 5.6 years (IQR 2.9–11.0). GAD antibody levels were elevated in 9.7% of participants; these were assigned to the SAID subgroup.

Cluster characteristics

Frequency distribution and characteristics of the clusters are presented in figure 1. Since the clusters formed had similar key characteristics to the ANDIS subgroups, we gave them the same names. One cluster was characterized by high HbA1c and low beta cell function similar to the SIDD subgroup in Ahlqvist *et al*'s study, one was characterized by high BMI and high insulin resistance similar to the SIRD subgroup, and two were characterized by either low age at diagnosis similar to the MOD subgroup, or high age at diagnosis similar to the MARD subgroup. The main difference from the original ANDIS clusters was that the MOD cluster did not have a particularly high BMI, and the insulin resistance was less severe in our SIRD cluster compared with that in ANDIS. The clusters all had Jaccard stability coefficients of >0.75, indicating stable clusters. When using ANDIS coordinates, the SIRD cluster was small (4.5%, online supplemental figure 3), and most of the participants who were assigned to the SIRD cluster formed in the 'de novo' analyses were assigned to the MOD and MARD clusters when using ANDIS coordinates (online supplemental table 1).

Table 1 Baseline characteristics of the study population (n=1899)

Baseline characteristic	
Women, n (%)	931 (49)
Age at participation, years, mean (SD)	65.6 (11.9)
Age at diabetes diagnosis, years, mean (SD)	57.6 (12.9)
Diabetes duration, years, median (IQR)	5.6 (2.9–11.0)
Family history of diabetes, n (%)	782 (56)
Physical examination	
BMI, kg/m^2, mean (SD)	29.6 (4.9)
Waist circumference, cm, mean (SD)	98 (13)
Waist-to-hip ratio, mean (SD)	0.92 (0.08)
Systolic blood pressure, mm Hg, mean (SD)	149 (24)
Diastolic blood pressure, mm Hg, mean (SD)	81 (14)
Laboratory measurements	
HbA1c, mmol/mol, median (IQR)	58 (48–72)
HbA1c, %, median (IQR)	7.5 (6.5–8.7)
Fasting glucose, mmol/L, mean (SD)	8.4 (2.5)
Fasting C-peptide, nmol/L, median (IQR)	0.8 (0.4–1.1)
HOMA2-B, %, median (IQR)	58 (36–87)
HOMA2-IR, median (IQR)	1.9 (1.1–2.9)
Elevated GAD antibodies (ai≥0.08), n (%)	185 (9.7)
LDL cholesterol, mmol/L, mean (SD)	3.6 (1.1)
Triglycerides/HDL cholesterol ratio, median (IQR)	1.8 (1.1–2.9)
eGFR, mL/min/1.73 m^2, mean (SD)	84 (19)
ALAT*, U/L, median (IQR)	29 (22–41)
CRP*, mg/L, median (IQR)	1.8 (0.8–4.3)

*Only measured in participants included at HUNT3 (n=593).
ai, antibody index; ALAT, alanine aminotransferase; BMI, body mass index; CRP, C reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA2-B, homeostasis model assessment of beta cell function; HOMA2-IR, homeostasis model assessment of insulin resistance; HUNT, Trøndelag Health Study; LDL, low-density lipoprotein.

Incidence of vascular complications and mortality

In analyses of incident diabetes complications, median follow-up time ranged from 9.1 years (IQR 3.6–13.2) for retinopathy to 13.0 years (IQR 8.1–17.8) for all-cause mortality, and 63.3% of participants died during the follow-up period. The incidence of retinopathy was higher in the SAID (HR 1.76 (95% CI 1.28 to 2.42)) and SIDD (HR 1.53 (95% CI 1.17 to 2.01)) subgroups, compared with the MARD subgroup (figure 2 and online supplemental table 2). For the SIDD subgroup, the excess risk disappeared when adjusting for baseline HbA1c. All-cause mortality and the incidence of chronic kidney disease were higher in the SIDD and SIRD subgroups. These increased risks disappeared for the SIDD subgroup when adjusting for baseline HbA1c, but not for the SIRD subgroup. The SIDD subgroup had increased incidence of stroke, and the SAID subgroup had lower risk of myocardial infarction, also in the adjusted models. Most of these results were similar when using clusters based on ANDIS centroids, but in these analyses, the MOD subgroup also had higher incidence of chronic kidney disease and all-cause mortality (online supplemental table 3). The prevalence and adjusted prevalence ratios for complications developed prior to HUNT participation are presented in

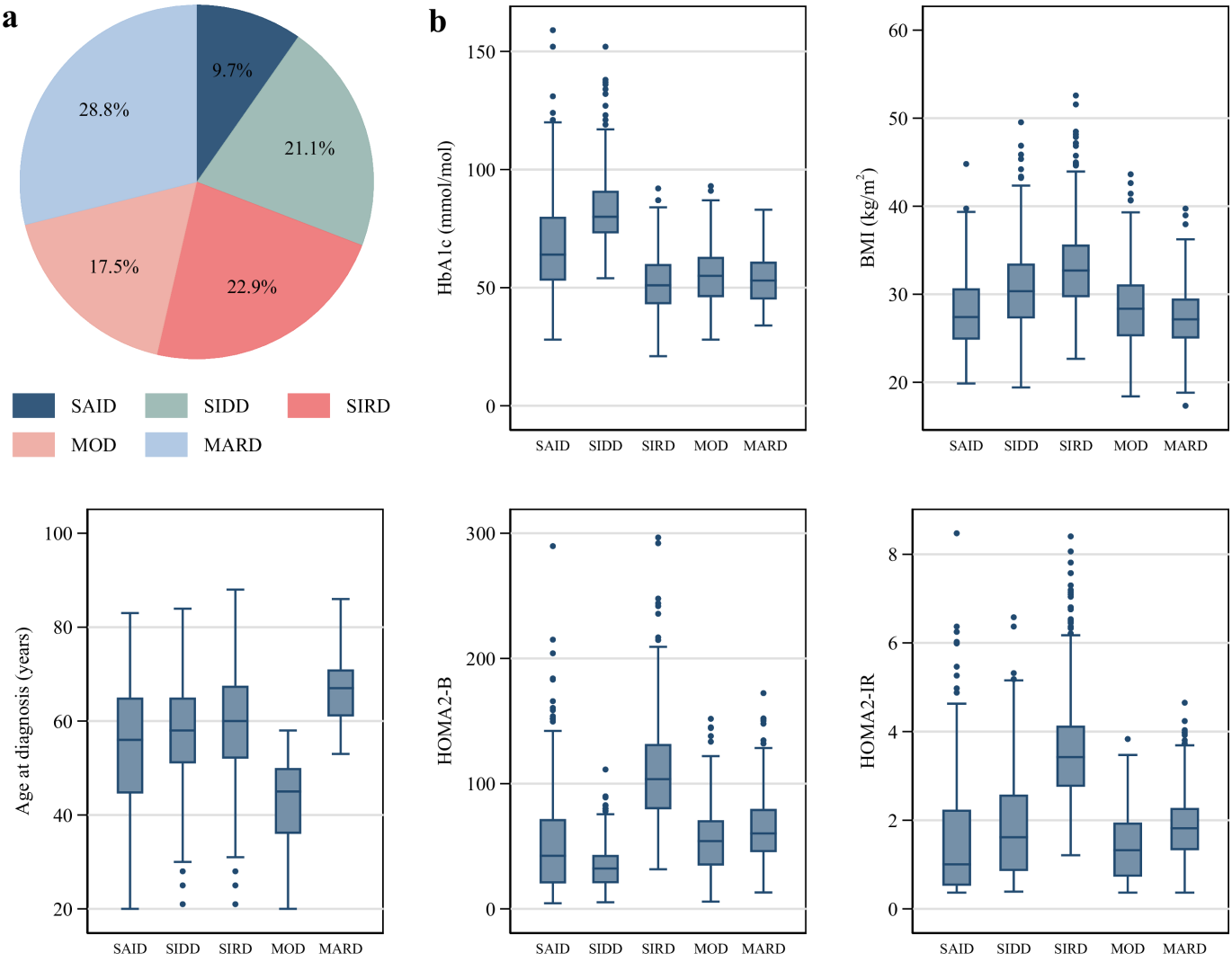

Figure 1 Frequency distribution of clusters (a) and box plot of cluster variables by cluster (b). BMI, body mass index; HOMA2-B, homeostasis model assessment of beta cell function; HOMA2-IR, homeostasis model assessment of insulin resistance; MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SAID, severe autoimmune diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes.

online supplemental table 4, and baseline cardiovascular risk factors and use of medication by subgroup are presented in online supplemental table 5.

Predictive ability of clusters

Figure 3 displays estimates for the discrimination ability (C-index) of clusters (both the clusters formed 'de novo' in this study, and those formed based on ANDIS cluster centers), and that of single continuous variables such as HbA1c or eGFR, or several continuous variables (either the five cluster variables or five cardiovascular risk factors). For retinopathy, the discrimination ability of the clusters (C-index 0.65) was slightly higher than the model including adjustment variables alone (C-index 0.64), but similar to that of the models including either HbA1c (C-index 0.65), C-peptide (C-index 0.66) or HOMA2-B (C-index 0.66) as continuous variables. For chronic kidney disease, the clusters yielded a C-index similar to that of triglyceride/HDL ratio (0.74), C-peptide (0.74), or HOMA2-IR (0.75). The models including either baseline eGFR alone or five cardiometabolic risk factors yielded slightly higher C-indexes (0.76 and 0.78, respectively). The estimated R^2, a measure of explained variance, gave similar indications as the C-index (online supplemental figure 4). For every outcome examined, the CIs for the C-index and R^2 were overlapping between the different models. The findings were similar in the subset of participants with short diabetes duration (<3 years since diagnosis, online supplemental figure 5).

Associations between clusters and duration of diabetes

Participants with longer duration of diabetes had higher HbA1c, and lower HOMA estimates of beta cell function (HOMA2-B) and insulin resistance (HOMA2-IR), compared with those with short duration of diabetes (all p<0.001, table 2). Similar results were found in age-standardized analysis (online supplemental table 6). The SIDD and MOD clusters were larger at longer diabetes duration, and the SIRD and MARD subgroups smaller. Using cluster centers from ANDIS to group our

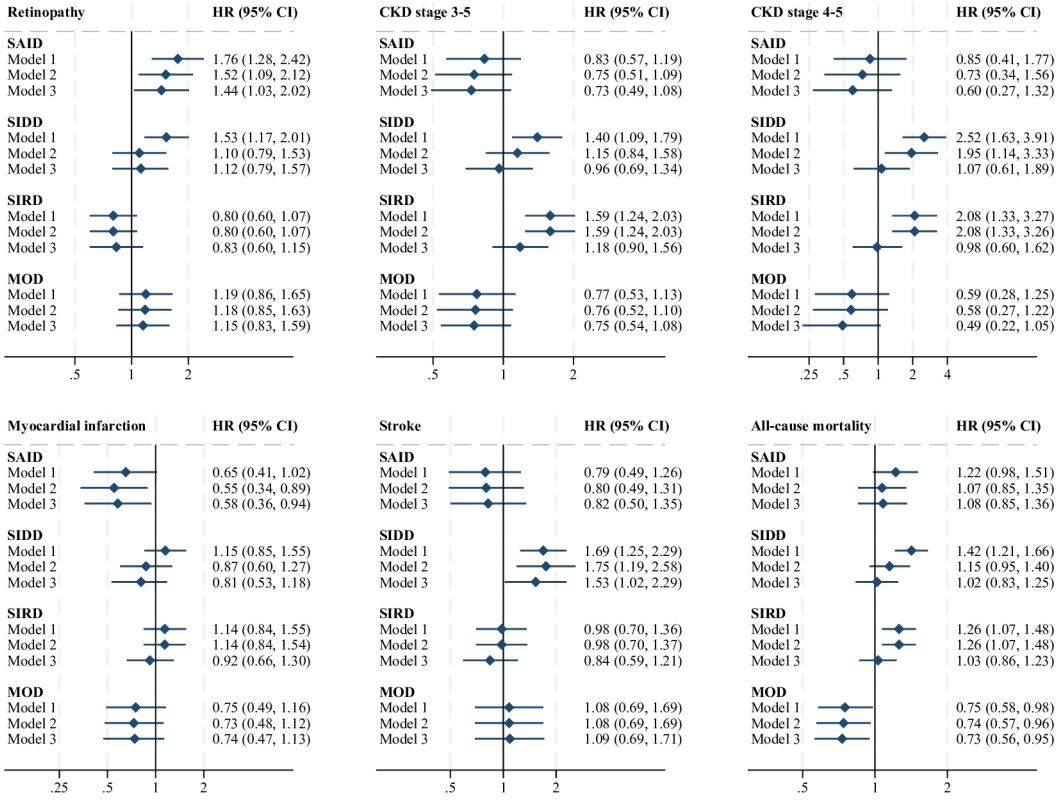

Figure 2 HRs for vascular complications by cluster. Mild age-related diabetes (MARD) is the reference group. Model 1: adjusted for sex, age, diabetes duration and time of inclusion (HUNT2 vs HUNT3). Model 2: model 1+HbA1c. Model 3: model 2+BMI, waist circumference, systolic and diastolic blood pressure, estimated glomerular filtration rate (eGFR), low-density lipoprotein (LDL) cholesterol, and triglyceride/high-density lipoprotein (HDL) cholesterol ratio. BMI, body mass index; CKD, chronic kidney disease; HUNT, Trøndelag Health Study; MOD, mild obesity-related diabetes; SAID, severe autoimmune diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes.

participants gave similar results. In the small subset of participants who had participated in both the HUNT2 and HUNT3 diabetes studies and did not have missing variables in either survey (n=119), 33% shifted cluster from HUNT2 to HUNT3 (online supplemental table 7). The proportion that changed cluster was highest in the SIDD (64%) and SIRD (50%) subgroups.

DISCUSSION

In this population-based prospective cohort study, we examined whether assigning individuals with adult-onset diabetes to data-driven clusters as suggested by Ahlqvist *et al* could provide more personalized prediction of late complications in a general diabetes population with varying diabetes durations. Across up to 25 years of follow-up, we confirmed associations between diabetes clusters and different risks of vascular complications; however, for most outcomes these differences disappeared when adjusting for HbA1c or for commonly measured cardiovascular risk factors. Finally, for every outcome, we found individual established risk factors to provide at least as good prediction as the diabetes clusters.

Several studies have demonstrated associations between the ANDIS clusters and diabetic complications, but few investigated whether these associations provide better prediction of outcomes than conventional risk factors. In an RCT population with up to 5 years of follow-up, Dennis *et al* found age at diagnosis to be better at predicting glycemic progression, and baseline eGFR to be better at predicting chronic kidney disease, compared with the clusters.[6] Lugner *et al* found nine cardiovascular risk factors combined (not including HOMA2 estimates or C-peptide) to be better at predicting CVD or mortality than four clusters formed based on the same nine variables (C-index 0.77 vs 0.66 for both CVD and mortality, with a median follow-up time of 5.2 years).[23] However, it is not so surprising that such continuous variables outperform clusters when age is not included as a covariate in the prediction models. Since age is the most important risk factor for several of the outcomes measured, when excluding age as a covariate, variables that have a strong association with age (such as age at diagnosis, eGFR and systolic blood pressure) could appear to have a mistakenly important predictive value. Thus, we chose to include age, sex and diabetes duration (variables that are usually readily available in a clinical or research setting) as adjustment variables in every model. This resulted in smaller differences in C-index and R^2 between models, since a large contribution to the prediction models was

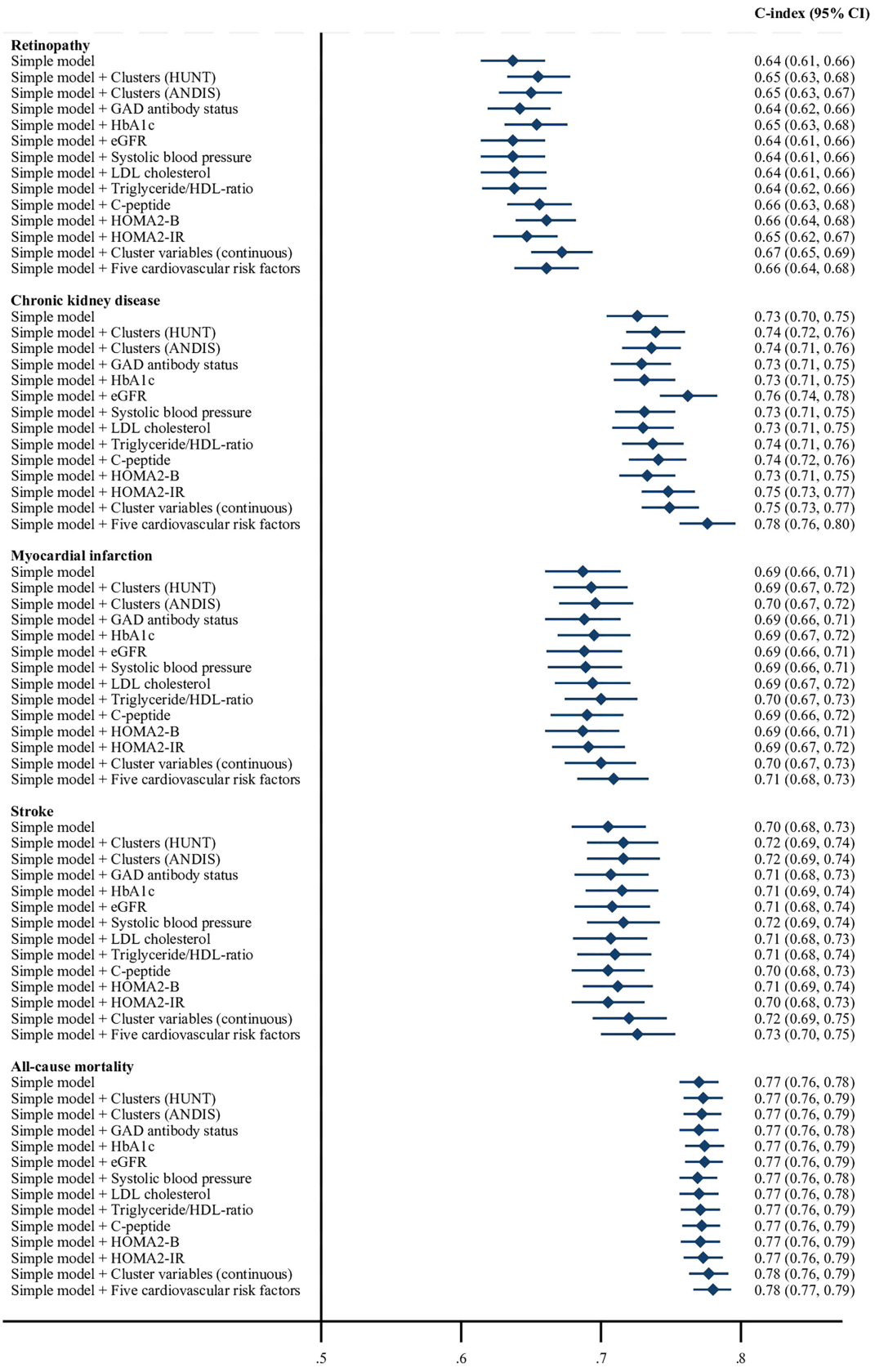

Figure 3 Estimated Harrell's concordance index (C-index) for models including clusters or established risk factors. Simple model: age, sex, diabetes duration and time of inclusion. Cluster variables: body mass index (BMI), HbA1c, homeostasis model assessment of beta cell function (HOMA2-B), and homeostasis model assessment of insulin resistance (HOMA2-IR). Five cardiovascular risk factors: BMI, systolic blood pressure, HbA1c, estimated glomerular filtration rate (eGFR), and triglyceride/high-density lipoprotein (HDL) cholesterol ratio. ANDIS, All New Diabetics in Scania; HUNT, Trøndelag Health Study; LDL, low-density lipoprotein.

Table 2 Baseline cluster variables and use of medication by duration of diabetes

	Diabetes duration		
	<3 years	3–10 years	>10 years
Number of participants (% of total)	502 (26)	815 (43)	582 (31)
Cluster variables			
HbA1c, years, median (IQR)	51 (43–61)	57 (49–70)	67 (55–80)
BMI, kg/m^2, mean (SD)	30.0 (5.2)	29.8 (4.8)	29.1 (4.7)
Age at diagnosis, years, mean (SD)	62 (12)	59 (12)	52 (13)
HOMA2-B, %, median (IQR)	72 (51–105)	58 (38–86)	44 (25–70)
HOMA2-IR, median (IQR)	2.2 (1.6–3.1)	2.1 (1.3–3.0)	1.4 (0.6–2.4)
Use of glucose-lowering medication, n (%)			
No medication	204 (46)	179 (25)	69 (14)
Oral medication only	212 (47)	391 (54)	183 (36)
Insulin	31 (7)	151 (21)	257 (50)
Cluster distribution, n (%)			
SAID	39 (8)	66 (8)	80 (14)
SIDD	38 (8)	174 (21)	188 (32)
SIRD	169 (34)	195 (24)	70 (12)
MOD	58 (12)	128 (16)	147 (25)
MARD	198 (39)	252 (31)	97 (17)

BMI, body mass index; HOMA2-B, homeostasis model assessment of beta cell function; HOMA2-IR, homeostasis model assessment of insulin resistance; MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SAID, severe autoimmune diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes.

provided by the adjustment variables alone. Still, clusters did not provide better prediction of vascular complications than established cardiometabolic risk factors as continuous variables. This was true both for clusters formed 'de novo' in our population, and for clusters formed based on cluster center coordinates from ANDIS. Even the models that included one single continuous clinical variable (in addition to the adjustment variables), such as HbA1c or fasting C-peptide, yielded performance estimates that indicated they performed at least as well as the clusters.

Although the original cluster analysis in ANDIS was performed in participants with short duration of diabetes, Ahlqvist *et al* suggested that clusters could be stable over time and demonstrated similar clusters in a cohort of participants with longer diabetes duration.[1] However, we found cluster variables to be associated with diabetes duration, in line with studies on diabetes pathophysiology demonstrating a progressive loss of beta cell function starting years prior to diagnosis and progressing throughout the course of disease,[24] and a gradual increase in HbA1c as the disease progresses, even when using glucose-lowering medication.[25] The fact that clusters were not stable over time could be a contributing explanation for their poor predictive ability.

Our study informs about the predictive utility of clusters when applied to a general adult population with varying diabetes durations, and the predictive ability may be better when cluster variables are obtained at the time of diagnosis. Nonetheless, we found similar results when we restricted our analysis to the 502 participants with short duration of diabetes. The association between cluster variables and diabetes duration could represent a problem to clustering in newly diagnosed individuals as well. Since time of diagnosis does not directly represent neither the time of onset of hyperglycemia, nor the onset of the disease processes leading up to the development of hyperglycemia,[24] cluster assignment in newly diagnosed individuals is also likely to, to some degree, reflect the duration of the pathological process underlying diabetes. For instance, it seems likely that some participants with a very high HbA1c at diagnosis have had a longer duration of undiagnosed diabetes.

In line with findings from previous studies, the SIRD subgroup had an increased risk of chronic kidney disease.[1 5 8] This increased risk persisted after adjusting for HbA1c. Furthermore, second to baseline eGFR, we found the variables associated with insulin resistance, such as HOMA2 estimates of insulin resistance, fasting C-peptide, and triglyceride/HDL ratio, to be the continuous variables that gave the highest C-index and R^2 for the prediction of chronic kidney disease. These findings support previous evidence indicating a link between insulin resistance and chronic kidney disease, independent of the degree of hyperglycemia.[26 27] On the other hand, the excess risks of complications for the SIDD subgroup seemed to a large degree to be mediated by their higher HbA1c, a well-established risk factor for

diabetic complications.[25] It should be noted that the association between the SAID subgroup and retinopathy persisted after adjusting for HbA1c and cardiovascular risk factors, which could indicate an association between beta cell insufficiency and an increased risk of retinopathy, regardless of glycemic control. In support of this, HOMA2-B and fasting C-peptide as continuous variables yielded similar C-indexes for retinopathy as HbA1c. However, although guidelines for screening for retinopathy are similar for patients with type 1 or type 2 diabetes, we cannot rule out that there are differences in follow-up between these groups of patients that could affect the time to retinopathy diagnosis.

For new subgroups to be implemented in clinical practice there should be robust evidence demonstrating their feasibility and utility in treatment, follow-up, or surveillance of patients. One should also consider the psychological impact for patients being assigned to a 'mild' or 'severe' subgroup of diabetes. The study by Ahlqvist *et al* has provided valuable insights into the heterogeneity of type 2 diabetes and its vascular complications and brought attention to the need for more personalized treatment of these patients. However, the results of our study suggest that the predictive value of the clusters, when derived from a general diabetes population with varying durations of the disease, is insufficient for clinical implementation aimed at predicting vascular complications. Our study did not investigate other potential uses of these clusters, such as their ability to predict treatment response to glucose-lowering medication.

Strengths and limitations

The population-based study design captures a general diabetes population, with all adult ages and durations of diabetes included, mimicking a clinical setting. Furthermore, linkage to local and national registers using unique national identity numbers provides the opportunity to follow-up all participants until the end of the study period, or until emigration or death, resulting in up to 25 years of follow-up. GAD antibodies were not measured at the time of diagnosis, but at the time of study participation. Thus, some participants with autoimmune diabetes and longer diabetes duration could have lost their GAD antibodies prior to the HUNT examination, resulting in misclassification.[28] However, the fact that the sensitivity analysis including participants with only short duration of diabetes yielded similar results could suggest that this potential misclassification does not substantially alter the results. The diagnoses of retinopathy, myocardial infarction and stroke relied on ICD codes from hospitals, private practicing specialists, and death certificates, which could result in some misclassification. The HOMA2 model to estimate insulin resistance and beta cell function has several limitations and has not been validated for use in persons on glucose-lowering medications.[29] Also, direct comparison of C-peptide levels and thus HOMA2 estimates between different laboratories can be challenging due to the use of different assays. However, these are common limitations to studies investigating diabetes subgroups based on HOMA2 estimates. At baseline, 27% of participants reported not using glucose-lowering medication, likely indicating a mild diabetes, and thus our follow-up time may have been too short to detect late complications in these. This proportion was, however, similar to findings from a population-based study from Norway with data from 2005 and 2014,[30] indicating that our sample may be representative for a general Norwegian diabetes population.

The use of insulin, oral glucose-lowering medications and antihypertensive medication differed between subgroups at baseline. We did not have information on the use of lipid-lowering medication, nor in changes in the use of medication during follow-up. It is possible that differences in treatment could mask or attenuate differences in risks of complications between subgroups and influence the estimates for the predictive abilities of clusters and other risk factors. However, if this is the case, it should be noted that the choice of glucose-lowering agents and the decision to start preventive medications for CVD must have been made without knowledge on the individuals' subgroup affiliation, indicating that physicians have been able to correctly identify high-risk individuals without using diabetes clusters.

Finally, recent studies have investigated diabetes clusters formed based on genetic information, and future studies will show if these genetic clusters may be useful for prediction of complications and feasible for clinical implementation.[2 31 32]

CONCLUSIONS

In a general diabetes population with up to 25 years of follow-up, cluster assignment did not provide better prediction of vascular complications or all-cause mortality compared with established risk factors.

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