Metabolic Trajectories Before Diabetes Diagnosis Across Subgroups: A Pooled Analysis of Prospective European Cohort Studies

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Summary

Background **Adult-onset diabetes comprises subgroups differing in pathophysiology, clinical presentation, and risk of comorbidities. We investigated early phenotypic differences between individuals who later developed diabetes, stratified by subgroup at diabetes diagnosis.**

Abbreviations: ALT, alanine transaminase; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; HOMA2-B, homeostatic model assessment 2 estimates of β-cell function; HOMA2-IR, homeostatic model assessment 2 estimates of insulin-resistance; IGR, insulin-glucose ratio; IGR120, insulin-glucose ratio at 120 minutes during OGTT; IGR30, insulin-glucose ratio at 30 minutes during OGTT; LDL, low density lipoprotein; MARD, moderate age-related diabetes; MOD, moderate obesity-related diabetes; OGTT, oral glucose tolerance test; SAID, severe autoimmune diabetes; SBP, systolic blood pressure; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes; TG, triglycerides; WHR, waist-to-hip ratio

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Methods We conducted a pooled analysis of nine prospective European cohorts with 3309 individuals developing incident diabetes and 13,963 age- and sex-matched controls without diabetes. Cases were assigned to previously defined cluster-based subgroups: severe autoimmune (SAID), insulin-deficient (SIDD), or insulin-resistant diabetes (SIRD), and moderate obesity- (MOD) or age-related diabetes (MARD). Clinical and metabolic characteristics were retroactively assessed for three time periods (>12, 6–12, 1–6 years) before diagnosis.

Findings Despite similarly high body mass index (BMI) in MOD and SIRD at diagnosis, MOD differed from controls already >12 years before diagnosis (31% higher than controls), while BMI increased progressively in SIRD (from 14% to 25% higher than controls). Compared to controls in period 1–6 years, age-, sex-, and BMI-adjusted insulin-glucose ratio was higher in SIRD, MOD and MARD at fasting (88%, 45% and 14%, respectively) and 120 min (110%, 70%, 26%) during an oral glucose tolerance test ($p < 0.0001$ for all), and the first-phase insulin-glucose ratio was higher in SIRD (23% [6; 43] $p = 0.0072$) but lower in SIDD (−30% [−37; −22], $p < 0.0001$) and MARD (−29% [−34; −24], $p < 0.0001$). The autoimmune subgroup SAID also exhibited features of metabolic syndrome. Despite differences in HOMA2-B and HbA1c at diagnosis, insulin and glucose levels did not differ significantly between the SIDD and MARD subgroups 1–6 years earlier suggesting a rapid deterioration in glycemic control in SIDD around diagnosis.

Interpretation Subgroups of diabetes display different trajectories of insulin resistance, insulin deficiency, and features of the metabolic syndrome before diagnosis.

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Keywords: Diabetes; Diabetes stratification; Precision medicine; Classification; Diabetes subtype; Diabetes subgroup

Introduction

Type 2 diabetes can be considered an umbrella term for a heterogeneous group of individuals who likely differ regarding underlying biological mechanisms together with environmental and genetic risk factors. As this heterogeneity is recognized to influence treatment response and risk of complications, international guidelines now emphasize the importance of individualized treatment strategies.[1]

We previously proposed a data-driven stratification of adult-onset diabetes into five subgroups with differing disease progression and risk of diabetes-related complications, suggesting different pathophysiological profiles.[2] Using unsupervised clustering based on age at diagnosis, BMI, HbA1c, presence of GAD-antibodies, and HOMA2 indices of insulin resistance and secretion, we identified subgroups of severe autoimmune (SAID), insulin-deficient (SIDD), and insulin-resistant diabetes (SIRD), as well as moderate obesity- (MOD) and age-related diabetes (MARD). This diabetes stratification has since been replicated in at least 22 studies including ~88 000 individuals of diverse ancestries, making it the most widely supported data-driven diabetes stratification to date.[3]

The SIDD subgroup had the highest HbA1c at diagnosis and early signs of diabetic retinopathy. Despite relatively good glycemic control, the SIRD subgroup had increased risk of kidney, liver and cardiovascular diseases, that often develop even before the diagnosis of diabetes.[2,4–7] The MARD subgroup had the mildest metabolic derangement. Both the SIRD and MOD subgroups suffered from obesity at diagnosis, with similar BMI, but the MOD subgroup had earlier age at diagnosis of diabetes, less insulin resistance, and fewer comorbidities.

Vast literature has shown risk factors for the development of type 2 diabetes. Metabolic risk factors like overweight, abdominal obesity, hypertension, and dyslipidemia may precede diagnosis by more than 15 years.[8,9] However, trajectories of glycemia and other metabolic features in individuals developing different diabetes subgroups remain largely unknown. To our knowledge, only one study on 215 individuals with diabetes has characterized these subgroups before diabetes onset.[10] We hypothesize that metabolic disturbances leading to diabetes differ between the cluster-based subgroups of adult-onset diabetes, and that this would reflect the impact of different pathophysiological pathways in the disease processes. We aimed at characterizing the pre-diabetic phenotype of the subgroups regarding known type 2 diabetes associated factors in longitudinal cohorts of individuals initially without diabetes.

Methods

Study design

We used longitudinal cohort studies to assign individuals diagnosed with diabetes to five previously defined subgroups and compared clinical and

Research in context

Evidence before this study

We searched Ovid Medline for articles citing the original 2018 publication, which first defined the novel diabetes subgroups. In addition, a structured search of Ovid Medline was performed using both MeSH terms and keywords. The search combined the MeSH term Diabetes Mellitus, Type 2 with keyword variants ("type 2 diabetes", "T2D"). Concepts related to stratification and classification were captured using the MeSH terms Precision Medicine, Classification, Disease Progression, and Cluster Analysis, together with keyword terms ("stratification", "classification", "subtype*", "subgroup*", "trajector*", "precision medicine", "personalized medicine"). These terms were combined using OR within each concept group and with AND between groups. Results were limited to studies published from 2018 to November 2025. We found one study on prediabetic phenotype in the new diabetes subgroups.

Type 2 diabetes is the culmination of metabolic dysregulation that can start several years before the glucose level reaches the diagnostic level for diabetes, which in turn can go unnoticed for years before actual diagnosis. Clinical type 2 diabetes represents a highly heterogeneous group of individuals regarding anthropometrics, metabolic disturbances, treatment response, and the development of comorbidities, some of which can start before the diagnosis of diabetes.

In 2018, a subgrouping based on cluster-analysis of clinical factors was introduced to disentangle some of the heterogeneity. Subsequently, these subgroups have been shown to exhibit different disease outcomes and comorbidities, some of which present early, even before the diagnosis of diabetes. As the subgroups represent different clinical phenotypes at diagnosis, it can be hypothesized that this is mirrored in their phenotype prior to diagnosis, but this has been examined in only one study so far. The key question of this study is whether subgroups of diabetes exhibit different phenotypic characteristics prior to diagnosis, and if so, could this information enhance the understanding of pathogenetic differences in diabetes subgroups and could any indicators serve as warning signs of more severe forms of diabetes.

Added value of this study

This is the first multi-country study with multiple OGTT time points prior to diagnosis addressing this research question. The results reveal that the diabetes subgroups follow different trajectories with varying degrees of metabolic syndrome long before diagnosis. Compared to individuals without diabetes, those with obesity-related diabetes exhibited substantially and consistently greater BMI than sex- and age-matched controls without diabetes more than 12 years prior to diagnosis, whereas individuals later to be diagnosed with autoimmune diabetes or severe insulin-resistant diabetes (SIRD) demonstrated a progressively increasing BMI towards diagnosis. The blunted fold change in the first phase insulin response during oral glucose tolerance test, considered characteristic in early stages of diabetes, was seen in all subgroups. However, differing from those who later ended up in other subgroups, those later becoming SIRD had a higher insulin-glucose ratio than matched controls not developing diabetes, indicating compensatory hyperinsulinemia (better beta-cell capacity) in response to marked insulin resistance.

Implications of all the available evidence

The evidence supports pathophysiological differences between the diabetes subgroups. Better understanding of disease mechanisms paves the way for developing tools for clinical practice.

Besides obesity, evaluating insulin secretion and sensitivity could inform tools in clinical practice to predict not only diabetes but also early comorbidities.

anthropometric phenotypes before diabetes diagnosis with matched controls who did not develop diabetes. The analysis focused on three time periods, defined based on current understanding of the progression of dysglycemia[8,9] and the availability of relevant data: 1–6 years ($Period_{1–6}$), >6 to ≤12 years ($Period_{6–12}$), or >12 years before diagnosis ($Period_{>12}$) as illustrated in Fig. 1.

Study cohorts

We included nine European prospective cohorts with data on phenotypes of interest prior to diabetes onset, and clinical information measured within 5 years after diagnosis to enable subgroup assignment of individuals with incident diabetes (cases). Each diabetes case was matched with 1–5 controls who did not develop diabetes (from the same cohort except for the DiabNorth study), based on sex, age (±5 years), and year of study entry (±10 years); individuals with impaired fasting glucose or impaired glucose tolerance were excluded if this information was available. We excluded diabetes cases with known secondary diabetes or maturity-onset diabetes of the young, if any of the clinical variables used for subgroup assignment were missing or more than 5 SD from the mean, and individuals on insulin treatment in cohorts where HOMA2 was calculated from fasting insulin. The majority of the study participants were of European descent.

The study comprises 3309 cases with retrospective data for at least one of the target periods (N for cases/controls; $Period_{1–6}$: 1250/4144; $Period_{6–12}$: 811/3692; $Period_{>12}$: 1248/6127) [Electronic Supplementary Material (ESM), Table S1]. The contributing cohorts, described in detail in the ESM, were: the Finnish Botnia Study,[11] The Prevalence, Prediction and Prevention of

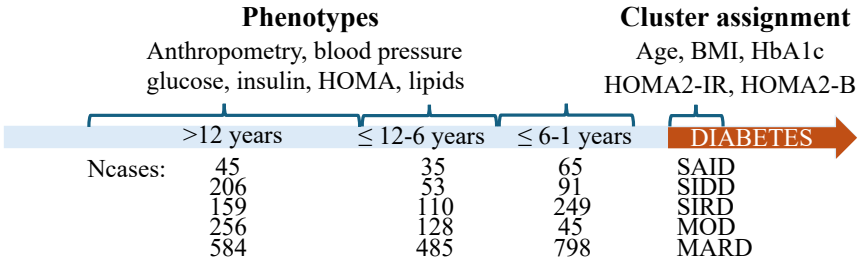

Fig. 1: **Study overview shows the maximum number of individuals for each subgroup (cases) in each study period.**

diabetes Botnia Study (The Botnia cohorts),[12] and The METSIM study[13]; the Danish The Inter99 Study[14]; the Swedish The DiabNorth,[15] The Malmö Preventive Project (MPP),[16] The MPP Rescreening, The Malmö Diet and Cancer (MDC),[17] and The MDC Rescreening (the Malmö cohorts); the Norwegian The HUNT Study,[18] and the German KORA study.[19] Availability of data across time periods and diabetes subgroups varied between cohorts (Table S1).

Phenotypes studied prior to diagnosis of diabetes

We included diabetes related phenotypes according to data availability before diabetes diagnosis: BMI (kg/m^2), waist-to-hip ratio (WHR), plasma/serum glucose (mmol/l) and insulin (pmol/l) at fasting, 30 min and 120 min during an oral glucose tolerance test (OGTT) (the standard time points for studying first phase insulin secretion and glucose tolerance), HOMA2 estimates of insulin resistance (HOMA2-IR) and beta-cell function (HOMA2-B), systolic (SBP) and diastolic (DBP) blood pressure (mmHg), serum low-density lipoprotein (LDL) cholesterol (mmol/l), high-density lipoprotein (HDL) cholesterol (mmol/l), triglycerides (mmol/l, TG), and alanine transaminase (U/l, ALT).

Data was harmonized by conversion to SI units when feasible. HOMA2 indices were calculated using either fasting plasma or serum C-peptide or insulin concentrations, using the software provided by the Radcliffe Department of Medicine, University of Oxford, UK.[20] Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula based on age, sex, and serum creatinine.[21] Individuals were excluded from analyses where data was missing.

Subgroup assignment

Individuals with diabetes were assigned to five previously defined cluster-based subgroups based on clinical variables measured within 5 years from diagnosis. Within each cohort, GAD antibody-positive cases were assigned to the SAID subgroup. The remaining cases were assigned to subgroups using, sex-specifically, the nearest centroid method, based on centroids derived from the original ANDIS cohort cluster analysis,[2] which has been shown to give 93% agreement with the original method.[7] Subgroup assignment was based on age at diagnosis, BMI, HbA1c, HOMA2-IR, and HOMA2-B. The use of HOMA indices for subtyping has previously been validated against gold-standard clamp methods.[20]

Statistical analysis

Analyses were performed separately for each cohort and time period using two approaches: 1) comparison of all cases with all controls; and 2) comparison of cases according to the future diabetes subgroup with their respective matched controls.

Linear regression was used for continuous variables (after natural log-transformation) and logistic regression for categorical variables. All models were adjusted for sex, age, and BMI at the time point (BMI analyses were adjusted for sex and age only). The results for each time period were pooled using a random-effects model with the restricted maximum likelihood (REML) method, implemented in the *metafor* package in R.[22] Results are reported only when at least two cohorts contributed data to the subgroup during the period. The results are reported as the difference [beta (95% confidence interval)] between the cases and the controls. The percent difference was estimated using the formula $(e^{beta}-1) \times 100$. A z-test was used to indirectly compare the effect sizes between subgroups, based on regression estimates and standard errors from separate models. A p-value of less than 0.01 (adjusted for five subgroups) was considered significant.

Ethics approval

Information regarding ethical approvals and patient consent procedures for each cohort is available in the description of each cohort in the referenced articles. Local principal investigators were responsible for contacting research ethics committees to obtain local or national approvals in accordance with applicable regulations, as well as seeking approvals from data protection officers.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In general, the metabolic profile of all the cases was unfavorable and reflected known risk factors for diabetes more than 12 years prior to diagnosis when compared with the controls (EMS Figures S1A–B, S2A–B, S3A, S4A, S5A–B, S6A, S7A–B, S8A, S9A–B).

Table 1 summarizes the characteristics of individuals at diagnosis of incident diabetes, stratified by diabetes subgroup. Data from the time of diagnosis is shown separately stratified for which prediabetes time-periods preceding diagnosis the individuals contributed to ($Period_{1–6}$, $Period_{6–12}$, $Period_{>12}$). In general, the cluster-based subgroups exhibited expected characteristic features with SAID and SIDD showing the lowest HOMA2-B and highest HbA1c, SIRD the highest HOMA2-IR and HOMA2-B, MOD the youngest age and the highest BMI, and MARD the oldest age as well as the lowest BMI and HbA1c level.

BMI and anthropometrics

Exact statistics for all pooled analyses can be found in Table S2–S3. The BMI increased compared to controls progressively toward diagnosis in the SAID and SIRD subgroups, while the MOD and MARD subgroups maintained a consistently higher BMI than the controls (Fig. 2A, ESM Figures S10–S12). The MOD subgroup showed the largest BMI difference compared to controls, exceeding their BMI by 31% [95% confidence interval (CI) 23; 38], 28% (20; 36), and 28% (21; 36) in $Period_{>12}$, $Period_{6–12}$, and $Period_{1–6}$, respectively. With the increasing trend the SIRD subgroup reached a similar difference compared to controls with a 25% (19; 31) higher BMI in $Period_{1–6}$.

The difference in BMI-adjusted WHR compared to controls was higher in SIRD at all periods. It was also significantly higher in the MARD subgroup up to 12 years before the diagnosis. The difference between MOD and controls appeared similar to SIRD at all time-points but the difference was not statistically significant (Fig. 2B, ESM Figures S13–S15). There were no significant differences between the non-autoimmune subgroups.

Glycemia and insulin secretion/resistance

All non-autoimmune subgroups had significantly higher fasting glucose levels than controls up to 12 years before diagnosis (Fig. 3A, ESM Figures S16–S18). During $Period_{1–6}$, the 30- and 120-min glucose response during an OGTT was higher compared with controls in all subgroups, without significant differences between them (Fig. 4A, ESM Figures S19 and S20). This could result from either a defective insulin secretory response or impaired insulin action.

The period prior to diagnosis	Data at diagnosis				
	SAID	SIDD	SIRD	MOD	MARD
1 to ≤6 years					
N (men %)	45 (50.0)	206 (64.0)	159 (71.5)	256 (51.0)	584 (62.0)
Age, years	64.0 (56.0–71.0)	60.90 (55.5–66.0)	65.2 (60.5–71.2)	52.4 (47.6–59.9)	68.8 (62.1–74.4)
BMI, kg/m2	28.5 (24.4–31.5)	26.2 (24.9–30.9)	32.5 (30.3–35.2)	35.6 (32.6–37.7)	27.4 (24.8–30.6)
HOMA2-B	57.5 (42.1–95.6)	39.2 (33.4–51.3)	132.7 (101.1–163.0)	93.9 (66.0–103.2)	73.1 (52.5–93.9)
HOMA2-IR	1.43 (0.90–2.20)	2.36 (1.00–3.28)	3.84 (3.19–4.59)	2.72 (1.66–3.27)	1.83 (1.20–2.65)
HbA1c, mmol/mol	50.0 (41.0–52.3)	77.2 (72.8–87.1)	46.4 (42.5–48.3)	45.9 (42.0–53.6)	46.9 (41.0–49.7)
>6 up to ≤12 years					
N (men %)	35 (62.5)	53 (70.0)	110 (54.1)	128 (40.1)	485 (60.9)
Age, years	64.2 (60.9–71.3)	62.0 (60.5–63.5)	68.1 (60.2–73.8)	53.5 (49.7–60.4)	67.4 (61.9–73.4)
BMI, kg/m2	27.0 (25.4–30.5)	28.9 (27.2–30.6)	32.6 (31.1–35.4)	35.6 (32.1–39.1)	28.0 (25.9–29.9)
HOMA2-B	63.6 (44.5–81.5)	26.8 (22.6–36.4)	140.4 (110.6–161.6)	86.1 (69.1–110.4)	80.2 (58.7–103.1)
HOMA2-IR	1.72 (1.32–2.48)	2.51 (1.67–3.29)	4.89 (4.00–6.35)	3.22 (2.56–3.81)	2.27 (1.78–2.79)
HbA1c, mmol/mol	50.8 (44.9–58.0)	99.0 (94.4–114.8)	47.7 (43.1–57.2)	50.0 (43.7–58.8)	47.7 (42.4–54.9)
>12 years					
N (men %)	65 (41.7)	91 (56.4)	249 (62.5)	45 (33.3)	798 (61.6)
Age, years	72.9 (66.7–77.5)	67.2 (63.1–72.6)	72.3 (67.4–77.0)	61.7 (59.0–65.0)	73.2 (68.5–77.8)
BMI, kg/m2	25.9 (23.3–30.2)	27.3 (23.9–41.4)	32.9 (30.6–35.9)	37.2 (35.9–40.2)	27.1 (24.7–29.8)
HOMA2-B	73.5 (37.2–98.1)	35.7 (14.4–35.1)	139.5 (122.1–164.0)	87.4 (71.4–107.3)	86.7 (64.6–107.5)
HOMA2-IR	1.97 (1.39–3.15)	2.56 (1.65–3.66)	4.50 (4.00–6.00)	3.18 (2.65–3.64)	2.26 (1.82–3.07)
HbA1c, mmol/mol	54.3 (46.7–70.1)	104.5 (98.8–118.5)	47.0 (43.4–53.0)	48.5 (46.6–55.5)	46.23 (42.04–50.4)

Data are shown as the median of the cohort medians (the median of 25% and 75% percentiles). BMI, body mass index kg/m^2; HOMA2-B, homeostatic model assessment 2 estimates of β-cell function; HOMA2-IR, homeostatic model assessment 2 estimates of insulin resistance; MOD/MARD, moderate obesity-/age-related diabetes; SAID/SIDD/SIRD, severe autoimmune/insulin-deficient/insulin-resistant diabetes. Note that the groups partly overlap, as a case may have been included for more than one pre-diagnosis period.

Table 1: **Pooled data (all cohorts) for the cases with incident diabetes from the time of diagnosis stratified for the subgroup of diabetes and for which pre-diagnosis period they were included in.**

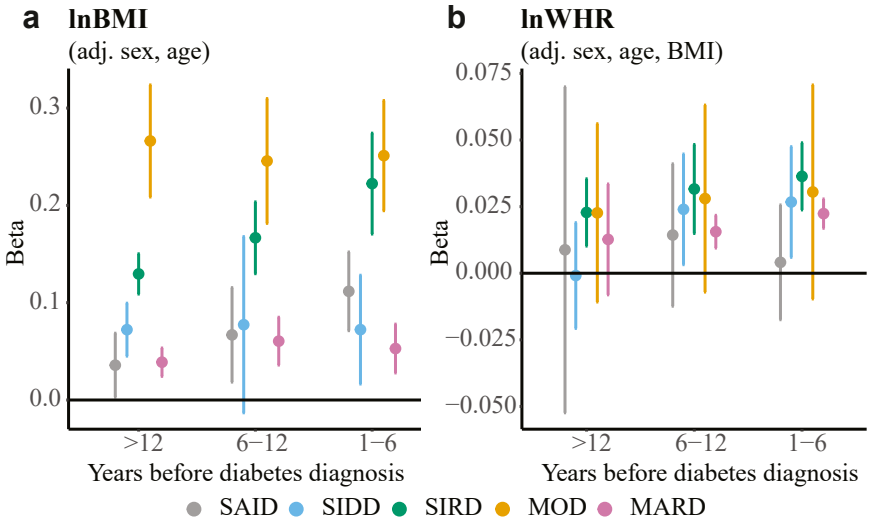

Fig. 2: **a) BMI (adjusted for age and sex), and b) waist-hip ratio (adjusted for age, sex and BMI) during Period$_{1–6}$, Period$_{6–12}$ and Period$_{>12}$.** The Y-axis shows the difference compared with control individuals (beta and 95% confidence interval). Results for individual cohorts can be found in ESM (ESM Figures S10–S15). BMI, body mass index; MOD/MARD, moderate obesity-/age-related diabetes; SAID/SIDD/SIRD, severe autoimmune/insulin-deficient/insulin-resistant diabetes; WHR, waist-hip-ratio.

In Period$_{1–6}$, the SIDD subgroup had 12% (2; 22) lower HOMA2-B value (reflecting insulin secretion at fasting) than controls (ESM Figure S6B, S21), but the difference was only nominally significant (p = 0.016). The 30-min insulin response during an OGTT as estimated by the insulin-glucose ratio (IGR30) and reflecting mostly first phase insulin secretion, was significantly lower in the SIDD [–30% (–37; –22)] and MARD [–29% (–34; –24)] subgroups compared to controls (Fig. 4B and ESM Figure S23). Distinctively, the SIRD subgroup had a significantly higher IGR30 compared to controls [23% (6; 43)] and the other subgroups (comparison p < 0.02 for SIRD vs. other subgroups). Across all subgroups, the fold-change in

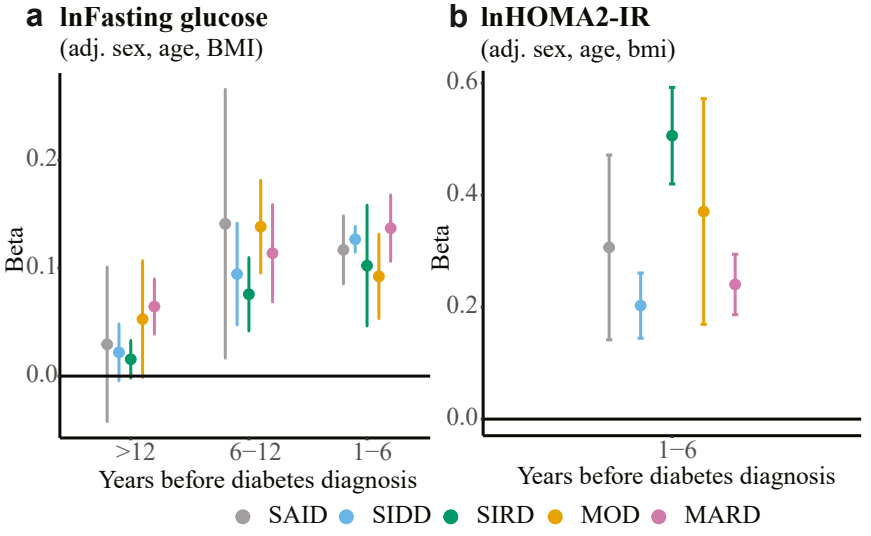

Fig. 3: **a) Fasting glucose during Period$_{1–6}$, Period$_{6–12}$ and Period$_{>12}$, and b) HOMA2-IR during Period$_{1–6}$ adjusted for sex, age and BMI.** The Y-axis shows the difference compared with control individuals (beta and 95% confidence interval). Results for individual cohorts can be found in ESM Figures S16–S19. BMI, body mass index; HOMA2-IR, homeostatic model assessment 2 estimates of insulin resistance; MOD/MARD, moderate obesity-/age-related diabetes; SAID/SIDD/SIRD, severe autoimmune/insulin-deficient/insulin-resistant diabetes.

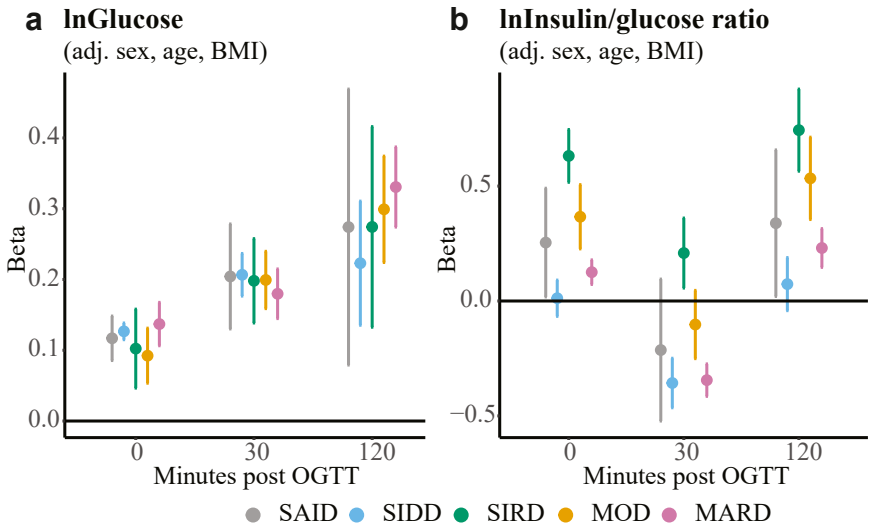

Fig. 4: **a) Glucose during OGTT, and b) insulin-glucose ratio adjusted for age, sex, and BMI during Period$_{1-6}$.** The Y-axis shows the difference compared with control individuals (beta and 95% confidence interval). Results for individual cohorts can be found in ESM (ESM Figures S20–S25). BMI, body mass index; MOD/MARD, moderate obesity-/age-related diabetes; SAID/SIDD/SIRD, severe autoimmune/insulin-deficient/insulin-resistant diabetes.

insulin-glucose ratio from fasting to 30 min was blunted but increased from 30 to 120 min (Fig. 4B, ESM Figures S22–S24).

Regarding fasting insulin resistance in Period$_{1-6}$, the HOMA2-IR was significantly higher in all subgroups compared to controls (Fig. 3B, ESM Figure S25), and the insulin-glucose ratio (IGR) in all subgroups except SAID and SIDD (Fig. 4B, ESM Figure S22). The SIRD subgroup showed the greatest difference, exceeding the level of the controls by 67% (52; 80) for HOMA2-IR and by 88% (68; 112) for fasting IGR, which differed significantly from the SIDD ($p = 1.1 \times 10^{-8}$) and MARD ($p = 3.1 \times 10^{-7}$) subgroups regarding HOMA2-IR and all other subgroups ($p < 0.004$) regarding IGR.

The Matsuda index reflects insulin sensitivity during an OGTT. As a mirror image of the HOMA2-IR pattern, the Matsuda index was lower in all subgroups compared to controls in period$_{1-6}$ (ESM Figures S3B, S26). The SIRD subgroup had the lowest level at −56% (−61; −50), which was statistically significant compared to the SIDD ($p = 6.8 \times 10^{-13}$) and MARD ($p = 1.2 \times 10^{-7}$) subgroups [−22% (−28; −15); −29% (−37; −21), respectively]. Also, the insulin-glucose ratio at 120 min during an OGTT (IGR120) was significantly higher in all subgroups except SAID and SIDD, compared to controls in Period$_{1-6}$, with no significant differences between subgroups (Fig. 4B, ESM Figure S24).

Lipids, liver enzymes and blood pressure

The triglyceride level was higher in all subgroups compared to controls during Period$_{1-6}$ (Fig. 5A, ESM Figure S7A, S27–S29) with the MOD subgroup showing the highest and MARD the lowest level [54% (31; 80) vs. 21% (14; 28), p = 0.0064]. The HDL cholesterol level was significantly lower in the SIRD, MOD, and MARD subgroups compared to controls already during Period$_{6-12}$, but there were no significant differences between the subgroups (Fig. 5B, ESM S7B, SS30-31).

The alanine transaminase level was higher in cases than in controls in Period$_{1-6}$, without significant differences between subgroups (ESM Figure S8, S32).

Systolic blood pressure was higher in all non-autoimmune subgroups compared to controls 1–6 years prior to the diagnosis (ESM Figure S9A, S9C, S33). Diastolic pressure was also significantly higher for the SIDD and MOD subgroups (ESM Figure S9B, S9D, S34). There were no significant differences in blood pressure between the subgroups.

Discussion

In this large, pooled analysis comprising over 3000 individuals with incident diabetes from nine European cohorts, we retroactively examined phenotypic differences observed before the diagnosis of diabetes. The individuals were stratified by cluster-based diabetes subgroups assigned within five years after diagnosis. We demonstrate abnormalities in metabolic syndrome related factors in all subgroups compared to individuals not developing diabetes more than 12 years prior to diagnosis, as well as different phenotypic trajectories between the subgroups prior to diagnosis.

Obesity is one of the strongest risk factors for both type 1 and type 2 diabetes.[23,24] We showed that all

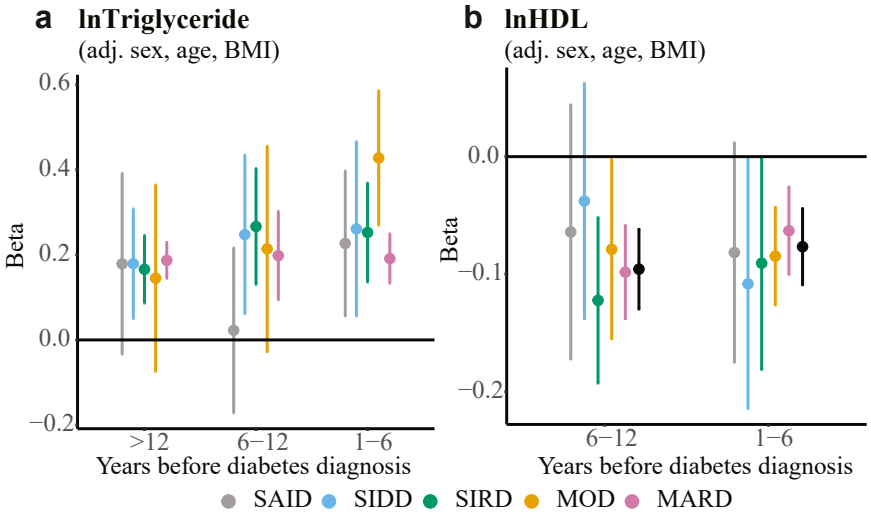

Fig. 5: **a) Triglycerides, and b) HDL adjusted for sex, age and BMI during $Period_{1-6}$, $Period_{6-12}$, and $Period_{>12}$.** The Y-axis shows the difference compared with control individuals (beta and 95% confidence interval). Results for individual cohorts can be found in ESM (ESM Figures S26–S27). BMI, body mass index; HDL, high density lipoprotein; MOD/MARD, moderate obesity-/age-related diabetes; SAID/SIDD/SIRD, severe autoimmune/insulin-deficient/insulin-resistant diabetes.

subgroups had higher mean BMI more than 12 years before diagnosis, compared to the age- and sex-matched controls, but the subgroups displayed different weight trajectories. Notably, in the MOD subgroup the BMI was as much as 25% higher compared to controls through all periods, whereas in the SAID and SIRD subgroups the BMI increased gradually toward diagnosis ending up at similar levels for the SIRD and MOD subgroups. The observed difference in BMI trajectories may have implications for future cardiovascular diseases, as the adverse effects of obesity on cardiac structure and function vary depending on the duration and severity of increased adiposity. There is evidence, for example, that higher adiposity from early adulthood onwards is associated with poorer systolic and diastolic function in older age independent of current adiposity.[25] Both the SIRD and MOD subgroups have been shown to have higher risk of heart failure and atrial fibrillation compared to other subgroups, in addition, SIRD had increased age- and sex-adjusted risk of incident myocardial infarction.[4] All in all, both obesity and insulin resistance impact cardiovascular diseases, with each condition contributing to cardiovascular risk through both distinct and overlapping mechanisms. The difference in weight trajectories could be interpreted as differences in the genetic risk for obesity and its interplay with environment between MOD and SIRD, as has been suggested.[5,26] The HUNT study has shown that polygenic risk for BMI plays a role in the development of obesity at different timepoints of life.[27] In the original ANDIS study, polygenic risk for BMI was most strongly associated with MOD while polygenic risk for BMI-adjusted WHR showed the strongest association with SIRD, but no association with MOD.[5] In the present study, sex and age adjusted WHR was higher compared to controls in all subgroups up to 12 years before diabetes, and even earlier in the more obese subgroups, but the differences were smaller than for BMI. Nominally, the SIRD subgroup had the highest BMI-adjusted WHR, which is in line with the known association between insulin resistance and visceral fat, but the difference was not significant compared to the other subgroups.

The fasting glucose level was higher in all subgroups compared to controls up to 12 years before diagnosis, and in MARD even earlier, supporting data from an earlier study reporting increased levels in all non-autoimmune subgroups (SAID was not included in the study) even 20 years before diagnosis.[10] Notably, the glucose level of the SIDD subgroup did not differ from the other subgroups during the years preceding diagnosis, although they were markedly more hyperglycemic (fasting glucose and HbA1c) at diagnosis. This suggests a rapid decline in metabolic control shortly before diagnosis and that the observed higher incidence of early-onset retinopathy in SIDD compared to other subgroups may rather derive from the severity or variability of hyperglycemia than its duration.[6,28]

Overall, the data suggests that the MARD subgroup develops diabetes slowly over a long period. While BMI was only a few percent higher than in the control individuals, signs of mild insulin resistance were present already >12 years before diagnosis and remained similar until diagnosis. Of note, even the SAID

subgroup, defined by GADA-positivity, had higher fasting glucose levels than the controls up to 12 years prior to diagnosis, suggesting a similar timeline of the development of diabetes as in the other subgroups. This is likely explained by the large proportion of antibody positive individuals without classical type 1 diabetes.

All subgroups were more insulin-resistant than the controls in $Period_{1–6}$, shown as higher fasting insulin and HOMA2-IR as well as lower Matsuda index during an OGTT. Regarding all measures, the SIRD subgroup seemed the most insulin-resistant, but the difference compared to MOD was not significant. The age-, sex- and BMI-adjusted HOMA2-IR was 50% higher in SIRD compared to controls, and the IGR120 as much as 74% higher, suggesting that these could be useful markers for early detection, possibly also for intervention. The observation of some degree of insulin resistance in all subgroups is partly in line with genetic data showing that while the distribution of the polygenic scores reflecting insulin secretion clearly differ, those for insulin resistance are shared by all non-autoimmune subgroups.[5] However, in our study, even the SAID subgroup exhibited insulin resistance.

The fold change in insulin response from fasting to 30 min was lower than in controls across all subgroups, consistent with a blunted first-phase insulin response, that has previously been shown in type 2 diabetes.[11] Despite this, the SIRD subgroup maintained a higher IGR30 than controls indicating compensatory hyperinsulinemia in response to marked insulin resistance. This early insulin response may reflect preserved beta-cell function in the context of severe insulin resistance, a hallmark of the SIRD subgroup.

While there were significant differences in the degree of obesity and insulin-resistance between the subgroups, this did not apply to other features of the metabolic syndrome, like high triglyceride and low HDL-cholesterol levels, or hypertension, which were similarly increased compared to controls in all subgroups, including SAID, across all time periods preceding diabetes. The elevated levels are consistent with prior studies showing that cholesterol levels begin to rise 15 years before diagnosis of diabetes and that low HDL-cholesterol is associated with both metabolic syndrome and type 2 diabetes.[8,29] Levels of LDL- and total cholesterol did not differ from controls at any time point; however, the effect of possible lipid-lowering medication could not be assessed. Antihypertensive medication, that we could not control for, could also mask differences between subgroups for blood pressure levels.

We acknowledge that the differences observed in our study are not sufficient for clinically relevant prediction of separate diabetes subgroups before onset. However, the observed metabolic differences prior to the diagnosis of diabetes, aligns with previous studies identifying clusters of individuals characterized by insulin resistance with high risk of kidney disease, cardiovascular disease, mortality as well as a high inflammatory load,[30] corresponding to the SIRD subgroup. These insights underscore the importance of recognizing metabolic diversity before diabetes onset based on repeated measurements and individual trajectories, as it may inform early risk stratification and targeted prevention, or treatment strategies. Our findings contribute to this growing body of evidence by showing that insulin resistance and beta-cell dysfunction are already evident across subgroups prior to diagnosis, suggesting that stratification based on metabolic traits may be clinically relevant even in the phase of intermediate hyperglycemia. Of the two subgroups showing early comorbidities, SIRD appears to have most potential for early identification, and thus possibly prevention of the comorbidities. It can also be speculated that some individuals phenotypically resembling the SIRD subgroup but with better beta-cell capacity, might never develop diabetes despite marked insulin resistance. They still might be at risk of cardiovascular complications and benefit from therapies like SGLT2-inhibitors and incretin mimetics.

A major strength of the study lies in its use of multiple well-established European cohorts, which provided access to longitudinal data spanning more than a decade prior to diabetes diagnosis. Compared to the only previously published study,[10] our study had a considerably larger sample size, and the inclusion of both fasting and glucose-stimulated insulin measurements allowed for a more nuanced assessment of insulin secretion and resistance patterns. Furthermore, the study design benefited from enhanced statistical power with multiple matched controls for each case, improving the reliability of subgroup comparisons.

However, several limitations should be acknowledged. Although the cases and controls had been studied and followed equally well within the study cohorts, the matched controls were expected to have a normal glucose tolerance throughout the follow-up (not implemented in all cohorts). This will likely render the controls metabolically healthier than all individuals without diabetes and could explain part of the difference in glucose levels. While the DiabNorth study incorporated a life-style intervention that could potentially influence metabolic trajectories, similar elements of intervention are inherent in all cohorts that measure metabolic parameters and provide feedback to participants, as this often involves lifestyle guidance. The effect of such intervention or possible medication effects could not be analyzed; however, we observed no systematic differences between DiabNorth and the other cohorts. Also, the number of individuals developing SAID was small, and the availability of data was uneven across cohorts and time points, and repeated measures were lacking. As a result, not all cohorts contributed equally to each time period or subgroup, which complicates longitudinal comparisons and

may introduce bias. Individuals, whose data was included in the earliest period (>12 years), were older at diagnosis, due to a selection bias in the Malmö cohorts, where C-peptide and GAD-autoantibodies were available only after 2007.

Further, while harmonization efforts were made, differences in cohort protocols and measurement techniques may have introduced variability in biomarker levels, potentially affecting subgroup classification or comparability across time points.

Another important limitation is not having data on confounding factors, such as comorbidities and medication. Medication commonly used in individuals without diabetes in the studied cohorts and time periods is unlikely to have significant effects on glucose and insulin levels, but lipid-lowering and antihypertensive medication could have influenced observed trends in cholesterol and blood pressure. This lack of information may have masked true differences between subgroups. Finally, the study population was predominantly of northern and central European ancestry, which limits the generalizability of the findings to other populations. While corresponding subgroups have been identified in other ancestries, differences in the clinical variables used for subgroup assignment necessitates population-specific tailoring of the method. Future studies are required to confirm these findings and should also aim to validate these trajectories in more diverse populations and explore the impact of early interventions tailored to subgroup characteristics.

Conclusion

This study demonstrates that phenotypic differences between subgroups of diabetes and controls without diabetes are evident more than a decade before diagnosis. These differences largely reflected subgroup characteristics at diagnosis. The most insulin-resistant subgroup, SIRD, exhibited marked insulin resistance and progressive weight gain, whereas the obesity-related subgroup was characterized by persistently high BMI from an early time point. Notably, the autoimmune SAID subgroup also displayed features of insulin resistance and the metabolic syndrome.

These findings underscore the heterogeneity of diabetes and highlight the potential of early identification of subgroup-specific risk profiles. Recognizing such patterns before diagnosis may inform targeted prevention strategies and personalized approaches to diabetes care.

Contributors

LH, EA, and TT designed the study, and MKA, LÄ, HM, MLa, OR, BOÅ, VL, PMN, CH, MR, TH contributed to the conception of the work. LH, EA, TT, MLe, RBP, AP, BTh, AL contributed to data collection. EA, LH, MKA, LÄ, HM, JV, TC, AM, BTa, and MCB performed the data analysis, LH, EA, and TT drafted the article. All authors contributed to the interpretation of data, and editing and critical revision of the article. All authors gave final approval of the version to be published.

Data sharing statement

Considering restrictions on IRB permissions, original de-identified data can only be available through specific reasonable requests and material transfer agreement following the EU regulations. The corresponding author or the cohort PIs can be contacted.

AI statement

Microsoft Copilot was used for language refinement. All AI-generated content was carefully reviewed and edited by the authors to ensure accuracy, clarity, and compliance with ethical standards. No AI tools were used to generate original scientific content, interpret data, or draw conclusions. The authors take full responsibility for the integrity and originality of the manuscript.

Declaration of interests

Torben Hansen reports stock or stock options: I own stocks in Novo Nordisk and Genmab. Rashmi B. Prasad reports support from grants paid to Institution (Lund University) and stock or stock options: AstraZeneca (own stock in AstraZeneca) and Novo Nordisk (own stock in Novo Nordisk). Michael Roden reports grants from Ministry of Culture and Science of the State of Northrhine Westphalia (MKW NRW) made to German Federal Ministry of Health (BMG), Federal Ministry for Research (BMBF) to the German Center for Diabetes Research (DZD e. V.) made to German Research Foundation (DFG, GRK 2576 Vivid) and European Community (HORIZON-HLTH-2022-STAYHLTH-02-01: Panel A) INTERCEPT-T2D consortium; consulting fees from Echosens, MSD and Target RWE; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AstraZeneca, made to Synlab, Boehringer Ingelheim, Eli Lilly, Madrigal and Novo Nordisk. EA reports research funding from AstraZeneca paid to institution. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2026.101715.

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