Predominantly genetic, intrauterine, and lifestyle aetiologies of type 2 diabetes are associated with distinct clinical presentations and risk of complications: a Danish cross-sectional and follow-up study

Aleksander Lühr Hansen,[a,b,*] Charlotte Brøns,[a] Leonie Mieke Engelhard,[a,b,c] Mette K. Andersen,[d] Jens Steen Nielsen,[e] Peter Vestergaard,[f] Kurt Højlund,[e] Michael Hecht Olsen,[g,h] Henrik Toft Sørensen,[b] Reimar W. Thomsen,[b] and Allan Vaag[a,c,i]

[a]Steno Diabetes Center Copenhagen, Herlev, Denmark
[b]Department of Clinical Epidemiology and Center for Population Medicine, Aarhus University Hospital, and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
[c]Lund University Diabetes Center, Lund University, Malmö, Sweden
[d]Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark
[e]Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark
[f]Steno Diabetes Center North Denmark, Aalborg University Hospital, Aalborg, Denmark
[g]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[h]Department of Medicine and Steno Diabetes Center Zealand, Holbæk Hospital, Holbæk, Denmark
[i]Department of Endocrinology, Skåne University Hospital, Malmö, Sweden

eClinicalMedicine 2026;97: 104029

Published Online 19 June 2026
https://doi.org/10.1016/j.eclinm.2026.104029

Summary

Background We investigated whether individuals who likely developed type 2 diabetes (T2D) through predominantly genetic, adverse intrauterine, or lifestyle aetiologies have different clinical presentations and complications.

Methods In this Danish nationwide combined cross-sectional and registry-based follow-up study, we included 7867 individuals with newly diagnosed T2D from the DD2 cohort, enrolled during 2010–2023 through general practices and hospital outpatient clinics across Denmark. Participants were required to have available genotyping and birthweight data; those with GAD antibody levels >30 were excluded. Individuals were grouped by presumed predominant aetiologies: genetic (highest-quartile T2D genetic risk score (GRS), birthweight above lowest quartile; n = 1435); intrauterine (lowest-quartile birthweight, GRS below highest quartile; n = 1195); and lifestyle (birthweight above lowest quartile, GRS below highest quartile; n = 4380). Baseline characteristics at diagnosis were examined using linear and log-binomial or robust Poisson regression. The main follow-up outcomes were standardised 10-year risks of major adverse cardiovascular events and microvascular complications after DD2 enrolment, estimated using the Aalen–Johansen method.

Findings Compared with the genetic group (18%), intrauterine (15%) and lifestyle (56%) aetiologies both showed −6.9% lower Homeostatic Model Assessment-2 (HOMA2) insulin sensitivity, higher triglycerides (+6.6% and +5.3%), higher HOMA2 beta-cell function (+8.9% and +9.6%), and higher high-sensitivity C-reactive protein (+14.8% and +24.1%). Age at T2D diagnosis was 1.2 years lower (intrauterine) and 2.3 year higher (lifestyle). The 10-year risk of major adverse cardiovascular events was 14.8% (intrauterine), 13.2% (lifestyle), and 11.5% (genetic), corresponding to absolute risk differences (RDs) of +3.3% (95% confidence interval [CI] 0.6, 6.0) for intrauterine, and +1.7% (95% CI −0.3, 3.6) for lifestyle, *vs.* genetic aetiology. The 10-year risk of microvascular complications was 25.9% (intrauterine), 25.4% (lifestyle), and 21.8% (genetic), yielding RDs of +4.1% (95% CI 0.7, 7.5) for intrauterine and +3.5% (95% CI 1.0, 6.1) for lifestyle aetiology.

Interpretation Individuals who developed T2D with predominant intrauterine or lifestyle rather than genetic aetiology exhibited distinct characteristics including higher long-term complication risks. Future studies should validate this framework in more diverse populations and assess whether these proxy-based aetiological domains can improve risk stratification and guide treatment.

*Corresponding author. Steno Diabetes Center Copenhagen, Borgmester Ib Juuls Vej 83, 2730 Herlev, Denmark.
E-mail address: aleksander.hansen@regionh.dk (A.L. Hansen).

Funding This work was funded by Danish Agency for Science, the Danish Health and Medicines Authority, the Danish Diabetes Association, the Region of Southern Denmark, the Swedish Research Council, the Novo Nordisk Foundation, the Swedish ALF for Region Skåne, the Crafoord Foundation, and the Swedish Diabetes Association.

Keywords: Type 2 diabetes; Disease heterogeneity; Life-course epidemiology; Genetic risk score; Birthweight; Intrauterine environment; Lifestyle-related risk; Insulin resistance; Vascular complications; Microvascular complications; Macrovascular complications

Research in context

Evidence before this study

There is an urgent need to elucidate heterogeneity in type 2 diabetes (T2D) to improve prevention, prognosis, and clinical care through more precision medicine-oriented approaches. Recent evidence suggests that T2D risk factors can be grouped into three different domains: genetic predisposition (reflected by T2D genetic risk score [GRS]), adverse intrauterine environment (reflected by low birthweight [LBW]), and unhealthy lifestyle (reflected by obesity), which additively contribute to T2D risk. A lower birthweight has been associated with earlier T2D onset, lower body mass index (BMI), and higher risk of both macro- and microvascular complications. In contrast, among individuals with T2D, carriage of the single most impactful genetic variant for T2D in Europeans, *TCF7L2* rs7903146, has been associated with earlier T2D onset, lower BMI, and lower risk of macrovascular complications. Furthermore, recent studies have shown that genetic variants affecting disease susceptibility across nine chronic diseases including T2D show only weak associations with subsequent disease-specific mortality.

To review the existing evidence, we searched PubMed from inception through March 1, 2026, without language restrictions, using the terms "type 2 diabetes," "birthweight," "genetic risk score," "lifestyle," "BMI," "prenatal environment," "disease course," "disease presentation," "microvascular complications," "macrovascular complications," "subgrouping," and "precision medicine." We found no previous studies investigating potential differences in clinical presentation and subsequent longitudinal disease course among individuals who developed T2D predominantly due to genetic, intrauterine, or lifestyle-related factors.

Added value of this study

We classified a large cohort of individuals newly diagnosed with T2D into three presumed predominant etiological domains defined by T2D GRS and birthweight. Individuals who likely developed T2D through predominantly prenatal or lifestyle aetiologies, rather than a genetic predisposition to T2D, had more severe clinical presentations at diagnosis and higher risks of subsequent micro- and macrovascular complications.

Implications of all the available evidence

Sub-classifying individuals with T2D by presumed predominant etiological domains (genetic, intrauterine, or lifestyle) may refine prognostic assessment at diagnosis and shape future therapeutic strategies. Future work should validate this framework in more diverse populations and assess whether it adds clinical value for risk stratification and treatment selection.

Introduction

Type 2 diabetes (T2D) aetiology is multifactorial[1] and can be broadly categorised into three domains: genetic predisposition; an adverse intrauterine environment influencing foetal development; and postnatal environmental lifestyle factors.[2] T2D genetic risk scores (GRSs), a proxy for genetic predisposition, summarise the cumulative effects of >1200 genetic variants.[3] Birthweight provides a proxy for the intrauterine environment.[4] The relative influence of postnatal lifestyle factors (including stress, unhealthy diet, smoking, and physical inactivity) potentially can be indirectly inferred by minimising the possible effects of genetic (GRS) and intrauterine (birthweight) factors. The three aetiological domains appear to additively influence T2D risk.[2]

Although this three-domain model might seem simplistic, several risk factors in each domain have clinically relevant commonalities. For instance, low birthweight (LBW) is a strong marker and potential mediator of the elevated cardiometabolic risk associated with adverse early-life exposures.[4,5] Similarly, most T2D susceptibility genes have been identified via their roles in elevating plasma glucose, primarily by impairing insulin secretion, either in absolute terms or relative to insulin action.[3] Finally, most lifestyle-related risk factors appear to influence T2D risk through effects on adiposity.[1]

We therefore hypothesised that individuals likely to have developed T2D predominantly via genetic predisposition, an adverse intrauterine environment, or

postnatal lifestyle factors would have differing clinical presentations at T2D diagnosis and throughout the disease course. In a cross-sectional and follow-up study of a large cohort of individuals newly diagnosed with T2D, we investigated the three aetiological domains' associations with clinical characteristics at time of diagnosis, including insulin secretion, insulin sensitivity, and comorbidities, and with complication risk as many as 10 years thereafter. Our framework was hypothesis-driven and intended to examine whether these broad life-course domains might help explain any heterogeneity in clinical presentation and disease course after T2D diagnosis.

Methods

Study design and population

The nationwide Danish Centre for Strategic Research in Type 2 Diabetes (DD2) cohort comprises individuals recently diagnosed with T2D, enrolled by general practitioners and hospital outpatient clinics since 2010.[6] The cohort characteristics have been reported,[6] described at www.dd2.dk, and in Supplementary Method: DD2 cohort description. Clinical providers identify individuals with a recent T2D diagnosis and complete an online questionnaire on lifestyle and clinical factors. Danish citizens unique civil registration numbers enable linkage to national health and administrative registries. To reduce potential inclusion of autoimmune diabetes, we excluded 139 individuals with glutamic acid decarboxylase (GAD) antibody levels >30. The derivation of the analytic sample is shown in Fig. 1.

A total of 10,162 individuals enrolled during 2010–2023 were genotyped with the Global Screening Array-24 v2.0 or v3.0 chip (Illumina, San Diego, CA, USA) and the Illumina GenCall algorithm. Quality control excluded individuals with sex mismatches, >3rd degree relatedness, >5% missing genotypes, heterozygosity outliers, and non-European ancestry. T2D genetic aetiology was assessed using a GRS based on 1289 genome-wide significance association signals, of which 1283 were polymorphic and 1279 were available in our data for score construction[3] (Supplementary Method: Genotyping).

Intrauterine environment

Each participant's birthweight, non-singleton birth status (if applicable), and term status were retrieved from independent records dating in the Danish National Archives and the Danish Medical Birth Registry, as previously described.[7,8]

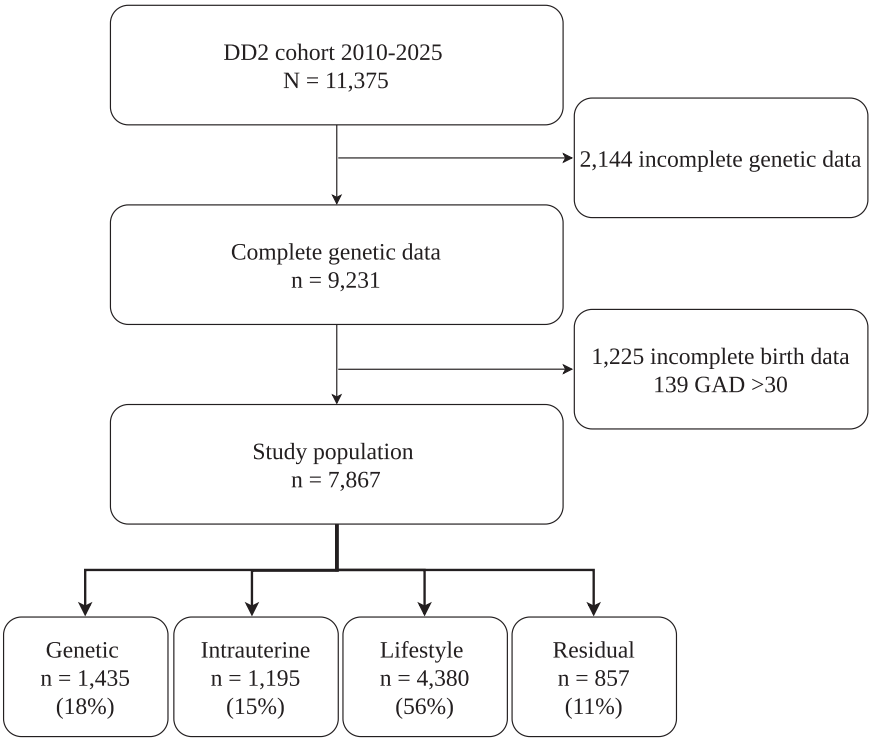

***Fig. 1:* Flowchart of study population. Legend:** Flowchart of study population and derivation of the aetiological groups. The analytic sample excluded individuals with incomplete genetic data, missing or incomplete birthweight data, and GAD antibody levels >30. Abbreviations: DD2 = Danish Centre for Strategic Research in Type 2 Diabetes; GAD = glutamic acid decarboxylase.

Sub-grouping of aetiological domains

Individuals were classified according to T2D GRS and birthweight. We assigned individuals in the highest GRS quartile within the DD2 cohort with a birthweight above the lowest quartile (≥3000 g) to the **genetic group**; those with a birthweight in the lowest quartile (<3000 g) and GRS below the highest quartile to the **intrauterine group**; and categorised the remaining individuals into a group with presumed predominant **lifestyle aetiology** (GRS below the highest quartile and birthweight above the lowest quartile) or into a residual **mixed/unclear aetiology** group. The residual group was retained for completeness but was not emphasised in the main interpretation because it did not represent one presumed predominant aetiological domain. The applied groups should be interpreted as proxy-based categories enriched for one presumed predominant aetiological domain relative to the others within an additive life-course framework, rather than as mutually exclusive biological subtypes or pure causal categories.

Clinical characteristics and outcomes

Clinical characteristics and outcome definitions are provided in Supplementary Table S1. Data on macro- and microvascular complications were obtained from the Danish National Patient Registry covering all Danish hospitals.[9] Death dates were retrieved from the Danish Civil Registration System. Cardiovascular disease (CVD) mortality was identified via the Danish National Patient Registry and Danish Registry of Causes of Death. Major adverse cardiovascular events (MACE) were defined as the first occurrence of myocardial infarction (MI), coronary revascularisation, stroke, or CVD death. For most CVD events, including MI and stroke which are acute events expected to be diagnosed at inpatient admissions, we considered only inpatient discharge diagnoses which have documented high predictive value in Denmark.[10,11] However, for heart failure (HF) and atrial fibrillation (Afib) that are often managed at hospital specialist outpatient clinics, we also included diagnoses from outpatient clinics and emergency department contacts without subsequent inpatient admission.[12] Microvascular complications were defined as the first occurrence of a hospital diagnosis of chronic kidney disease (CKD), neuropathy, or retinopathy. CKD was additionally defined based on non-emergency outpatient laboratory tests according to Kidney Disease Improving Global Outcomes (KDIGO) criteria (first occurrence of the second of two estimated glomerular filtration rate test values < 60 ml/min/1.73 m^2 or two urine albumin-creatinine ratio test values > 30 mg/g, recorded 90–365 days apart).[13,14] These data were obtained from the Danish National Laboratory database.[15]

Statistical analysis

We investigated the prevalence of the four etiological domain groups at T2D diagnosis. Descriptive data are reported as medians and interquartile ranges (IQRs) for continuous variables and as counts and percentages for categorical variables. Cross-sectional differences at diagnosis were examined using linear regression for continuous variables and log-binomial or robust Poisson regression[16] for categorical variables to estimate prevalence ratios (PRs), with the genetic group as the reference. We preferred PRs to odds ratios because several baseline categorical outcomes were common and PRs were therefore more directly interpretable. Assumptions of the linear regression models were assessed by inspection of residual and diagnostic plots. Longitudinal complication risks were analysed with Cox proportional hazard models to estimate cause-specific hazard ratios (HRs). Proportional hazards assumption was assessed using Schoenfeld and Martingale residuals. Standardised 10-year absolute risks were estimated using the Aalen–Johansen estimator, treating all-cause death as the competing event for non-fatal outcomes except MACE and death from CVD, for which non-CVD death was treated as the competing event. For all-cause mortality, the Kaplan–Meier estimator was used. For each outcome, follow-up started at DD2 enrolment and continued until the outcome of interest, death, emigration, or end of follow-up on February 2, 2025, whichever occurred first. The median follow-up duration was calculated as the time from DD2 enrolment until death, emigration, or the end of follow-up February 2, 2025. To account for potential confounders, we applied the parametric G-formula,[17] analogous to direct standardisation.[18,19] For each outcome, we fitted two cause-specific Cox regression models: one for the outcome of interest and one for the competing event. Using these models, we estimated absolute risks for each exposure group standardised to the covariate distribution of the full cohort. Standardised risk differences (RDs) were then calculated for the intrauterine and lifestyle groups *vs.* the genetic group. These standardised absolute risks and RDs represent weighted averages of the conditional averages within each confounder stratum. Non-parametric bootstrapping with 10,000 samples was used to obtain 95% confidence intervals (CI).[18] Our main models were adjusted for sex, calendar birth year, age, T2D duration at enrolment, and genetic principal components. We avoided additional adjustments in the main model to prevent overadjustment for intermediate factors, because the genetic and intrauterine domain exposures were present from birth onward. Exploratory analyses additionally adjusted for lifestyle behaviours (physical activity, smoking status, and alcohol consumption), socioeconomic markers (marital status and rural-urban residence), BMI, Haemoglobin (Hb)A1c, and number of glucose-lowering and antihypertensive medications (treatment intensity). These additional models were exploratory because several of these variables could be considered intermediates rather than confounders and

were therefore added in sequence spanning from less to more likely mediators (Supplementary Fig. S1). Log-transformed variables are presented as percentage changes. Missing data were imputed using multivariate imputations by chained equations via the R package MICE,[20] with parameters estimated separately in each imputed dataset and then pooled using Rubin's rules. The missingness was 0%–54%, with a median missingness of 10% for all covariates with any missing values. The missingness distribution was similar across all groups, sex, and age at enrolment (further detailed in Supplementary Methods: Multivariate imputations by chained equations (MICE) model specification). No formal sample size determination was performed as the sample size was determined by the number of eligible DD2 participants with available genotyping and birthweight data during the study period.

All analyses were performed in R version 4.4.3 (R Foundation for Statistical Computing), using the packages survival, riskRegression, prodlim, cmprsk, mice, sandwich, and lmtest. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Additional and sensitivity analyses

We repeated Cox regression models excluding individuals with a prior CVD history to assess associations in CVD-naïve individuals. To assess the effects of genetically determined birthweight, genetically determined BMI, and preterm status, we further adjusted our main models with a polygenic risk score (PGS) for birthweight[21] and a PGS for BMI,[22] as well as the born-at-term covariate. We reanalysed the results using a broader T2D PGS.[22] Unlike the main T2D GRS, these broader PGSs included variants beyond genome-wide significance. To test the robustness of our results and chosen sub-division criteria, we further divided the cohort into new groups according to the following cut-offs: genetic, highest quartile of GRS with birthweight over the median (>3400 g); intrauterine, below the median GRS and birthweight in the lowest quartile (<3000 g); lifestyle, below the median GRS and birthweight above the median; genetic/intrauterine, highest quartile of GRS and birthweight in the lowest quartile (<3000 g); and residual, the remainder.[22] To explore potential heterogeneity by sex, we post-hoc additionally performed exploratory sex-stratified Cox regression analyses.

Ethics

This DD2 study was approved by the Danish Data Protection Agency (record number 2008-58-0035), the Regional Committees on Health Research Ethics for Southern Denmark (record number S-20100082), and the Danish National Center for Ethics (record number 2308518). All cohort participants provided written informed consent to participate in the DD2 study.

Role of the funding source

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

Results

In total 7867 individuals with newly diagnosed T2D were allocated either to the genetic (18%; n = 1435), intrauterine (15%; n = 1195), lifestyle (56%; n = 4380), and residual (11%; n = 857) etiological domains, respectively (Fig. 1). The median age at enrolment was 61.5 years, the median diabetes duration was 0.9 years, 6.5% were diagnosed with T2D before age 40 years, and 41.7% were women. In crude numbers, the intrauterine group included more women and fewer married or partnered individuals. Lifestyle group members were more likely to be heavy alcohol drinkers, current smokers, and physically inactive (Table 1). Further descriptive data on metabolic profile, medication usage, and comorbidities at T2D diagnosis are provided in Supplementary Tables S2 and S3.

Compared with the genetic aetiology group, the intrauterine group was 1.2 years (95% confidence interval [CI] 0.4, 2.1) younger at T2D diagnosis. The lifestyle group was 2.3 years (95% CI 1.7, 3.0) older (Fig. 2), had a 1.9 kg/m^2 (95% CI 1.5, 2.3) higher BMI at enrolment, a 1.8 kg/m^2 (95% CI 1.2, 2.8) higher BMI at 20 years of age, and a 3.7 cm (95% CI 2.9, 4.5) larger waist circumference at T2D diagnosis (Fig. 2, Supplementary Table S4). Further explorative adjustments for alcohol consumption, smoking status, physical activity, socioeconomic markers (marital status and rural-urban residence), BMI at enrolment, HbA1c, and number of glucose-lowering medications attenuated the intrauterine group's association with younger age at T2D diagnosis, whereas all associations remained robust for the lifestyle group (Supplementary Table S4).

Compared with the genetic group, the intrauterine group had 6.6% (95% CI 1.7, 11.8) higher triglycerides, 4.3% (95% CI 0.7, 7.8) lower low-density lipoprotein (LDL) cholesterol, and 2.2% (95% CI –0.1, 4.5) lower HDL cholesterol, whereas the lifestyle group had 5.3% (95% CI 1.4, 9.3) higher triglycerides and 2.8% (95% CI 1.1, 4.6) lower high-density lipoprotein (HDL) cholesterol (Fig. 3). Further explorative adjustments halved the association with triglycerides and HDL cholesterol for the lifestyle group (2.9% [95% CI –0.9, 6.8] and 1.1% [95% CI –0.7, 2.8], respectively). Other associations remained after further adjustments, although the effects on HDL cholesterol became more imprecise and decreased to 1.8% (95% CI –0.5, 4.0) lower HDL cholesterol than observed in the genetic group (Supplementary Table S4).

Metabolic variables

Compared with the genetic group, the intrauterine group had 7.1% (95% CI 1.9, 12.5) higher C-peptide,

Enrolment characteristics	Genetic (n = 1435)	Intrauterine (n = 1195)	Lifestyle (n = 4380)	Residual (n = 857)	Total (n = 7867)
Sex					
Female	575 (40.07)	580 (48.54)	1604 (36.62)	441 (51.46)	3200 (40.68)
Age at enrolment (years)					
Median [IQR]	60.63 [51.05, 68.20]	58.74 [50.61, 65.85]	62.91 [54.43, 69.10]	58.92 [50.10, 66.53]	61.48 [52.53, 68.36]
Age at diagnosis (years)					
Median [IQR]	58.39 [49.24, 66.28]	56.85 [48.97, 64.32]	61.04 [52.68, 67.23]	56.81 [48.22, 64.67]	59.58 [50.88, 66.48]
Diabetes duration (years)					
Median [IQR]	0.96 [0.21, 2.69]	0.69 [0.12, 2.43]	0.89 [0.17, 2.61]	0.97 [0.19, 2.72]	0.88 [0.17, 2.62]
Family history of type 2 diabetes: number of affected relatives (n)					
0	602 (41.95)	624 (52.22)	2225 (50.80)	397 (46.32)	3848 (48.91)
1	462 (32.20)	360 (30.13)	1351 (30.84)	290 (33.84)	2463 (31.31)
2	266 (18.54)	156 (13.05)	593 (13.54)	132 (15.40)	1147 (14.58)
3+	105 (7.32)	55 (4.60)	211 (4.82)	38 (4.43)	409 (5.20)
Birthweight (g)					
Median [IQR]	3500 [3,300, 3800]	2700 [2,450, 2850]	3500 [3,300, 3820]	3000 [2,700, 3000]	3400 [3,000, 3700]
Preterm birth	55 (3.83)	566 (47.36)	114 (2.60)	205 (23.92)	940 (11.95)
BMI (kg/m^2)					
Median [IQR]	30.11 [27.04, 34.19]	30.52 [26.94, 34.69]	31.51 [27.76, 36.13]	30.69 [27.50, 34.64]	31.05 [27.47, 35.49]
Missing	697	544	2023	402	3666
BMI at 20 years of age (kg/m^2)					
Median [IQR]	23.89 [21.74, 26.42]	23.61 [21.01, 26.30]	23.71 [21.50, 26.12]	23.15 [20.6, 25.7]	23.67 [21.39, 26.22]
Missing	533	427	1616	310	2886
Waist circumference (cm)					
Median [IQR]	107 [101, 114]	107 [100, 115]	109 [102, 118]	107 [100, 115]	108 [101, 117]
Missing	5	7	27	6	45
Alcohol consumption (units per week)					
≥21/14	86 (5.99)	57 (4.78)	312 (7.12)	42 (4.90)	497 (6.32)
Smoking status					
Never	318 (48.18)	290 (54.21)	986 (47.36)	201 (48.32)	1795 (48.61)
Former	225 (34.09)	152 (28.41)	714 (34.29)	114 (27.40)	1205 (32.63)
Current	117 (17.73)	93 (17.38)	382 (18.35)	101 (24.28)	693 (18.77)
Missing	775	660	2298	441	4174
Physical activity (days per week)					
0	168 (11.71)	165 (13.82)	677 (15.46)	124 (14.47)	1134 (14.42)
1–2	276 (19.23)	267 (22.36)	900 (20.55)	179 (20.89)	1622 (20.62)
3–4	363 (25.30)	287 (24.04)	977 (22.31)	193 (22.52)	1820 (23.14)
5–6	241 (16.79)	195 (16.33)	673 (15.37)	134 (15.64)	1243 (15.80)
7	387 (26.97)	280 (23.45)	1152 (26.31)	227 (26.49)	2046 (26.01)
Marital/civil status					
Married/partnership	904 (65.22)	691 (60.45)	2637 (62.30)	499 (60.48)	4731 (62.36)
Divorced/separated	198 (14.29)	198 (17.32)	696 (16.44)	142 (17.21)	1234 (16.26)
Widow/widower	101 (7.29)	69 (6.04)	365 (8.62)	68 (8.24)	603 (7.95)
Not married/no registered partnership	183 (13.20)	185 (16.19)	535 (12.64)	116 (14.06)	1019 (13.43)
Missing	49	52	147	32	280
Rural/urban residence					
Capital municipalities	214 (14.92)	197 (16.50)	631 (14.41)	128 (14.94)	1170 (14.88)
Large city municipalities	321 (22.38)	242 (20.27)	936 (21.37)	197 (22.99)	1696 (21.56)
Provincial municipalities	364 (25.38)	290 (24.29)	1078 (24.61)	224 (26.14)	1956 (24.87)
Surrounding area municipalities	296 (20.64)	258 (21.61)	942 (21.51)	175 (20.42)	1671 (21.25)
Rural area municipalities	239 (16.67)	207 (17.34)	793 (18.11)	133 (15.52)	1372 (17.44)
T2D GRS					
Median [IQR]	1.17 [0.91, 1.57]	−0.31 [−0.87, 0.16]	−0.35 [−0.89, 0.14]	0.87 [−0.01, 1.28]	−0.02 [−0.68, 0.70]
T2D PGS					
Median [IQR]	0.41 [−0.17, 1.14]	−0.19 [−0.81, 0.47]	−0.17 [−0.82, 0.51]	0.25 [−0.45, 0.93]	−0.02 [−0.67, 0.68]
BMI PGS					
Median [IQR]	0.28 [0.07, 0.47]	0.25 [0.04, 0.43]	0.24 [0.03, 0.44]	0.24 [0.02, 0.46]	0.25 [0.04, 0.44]

(Table 1 continues on next page)

Enrolment characteristics	Genetic (n = 1435)	Intrauterine (n = 1195)	Lifestyle (n = 4380)	Residual (n = 857)	Total (n = 7867)
(Continued from previous page)					
Birthweight PGS					
Median [IQR]	−0.08 [−0.17, 0.00]	−0.12 [−0.21, −0.03]	−0.07 [−0.16, 0.02]	−0.13 [−0.22, −0.03]	−0.08 [−0.18, 0.00]

Legend: T2D GRS, T2D PGS, BMI PGS, and birthweight PGS are scaled and centred. Abbreviations: T2D = type 2 diabetes, GRS = genetic risk score, PGS = polygenic risk score, BMI = body mass index, IQR = interquartile range.

Table 1: **Baseline characteristics of 7867 individuals with newly diagnosed type 2 diabetes, by predominant aetiological group, Denmark, 2010–2023.**

8.9% (95% CI 4.9, 13.0) higher Homeostatic Model Assesment-2 (HOMA2)-β, 6.9% (95% CI 3.0, 10.7) lower HOMA2 insulin sensitivity (IS), and 14.8% (95% CI 4.9, 25.8) higher high-sensitivity C-reactive protein (hsCRP) at T2D diagnosis (Fig. 3), whereas the lifestyle group had 8.3% (95% CI 4.2, 12.5) higher C-peptide, 9.6% (95% CI 6.5, 13.) higher HOMA2-β, 6.9% (95% CI 3.8, 9.9) lower HOMA2-IS, and 24.1% (95% CI 15.7, 33.2) higher hsCRP (Fig. 3). Further explorative adjustments did not substantially change the associations for the intrauterine *vs.* genetic groups. However, for the lifestyle group, estimates of C-peptide, HOMA2-IS, HOMA2-β, and hsCRP were halved, specifically after adjustment for BMI (Supplementary Table S4).

Medication usage and prevalent complications

Compared with the genetic group, the intrauterine and lifestyle groups had greater use of antihypertensive medication (PR for three or more medications 1.52 [95% CI 1.30, 1.78] and 1.25 [95% CI 1.10, 1.42],

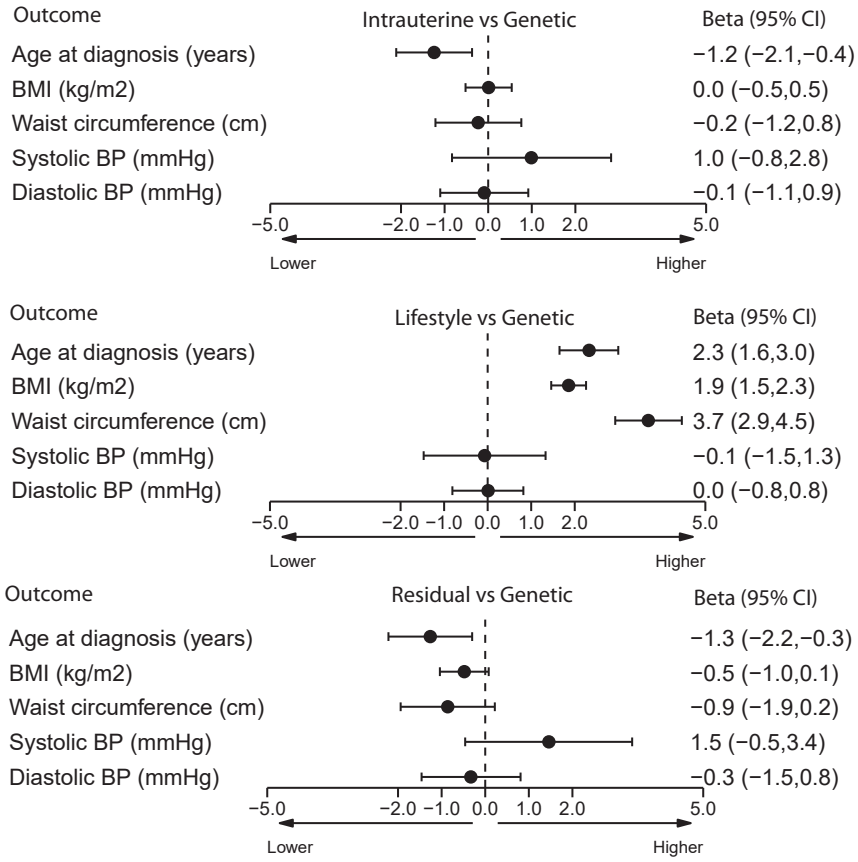

Fig. 2: **Linear regression analysis of age at diagnosis, anthropometric measures, and blood pressure. Legend:** Linear regression analysis according to phenotype groupings, with the genetic group as reference. Points represent beta estimates and horizontal error bars represent 95% confidence intervals. All models are adjusted for sex, calendar birth year, age at DD2 enrolment (except age at diagnosis), diabetes duration, and genetic principal components. Abbreviations: BMI = body mass index; BP = blood pressure; CI = confidence interval; DD2 = Danish Centre for Strategic Research in Type 2 Diabetes.

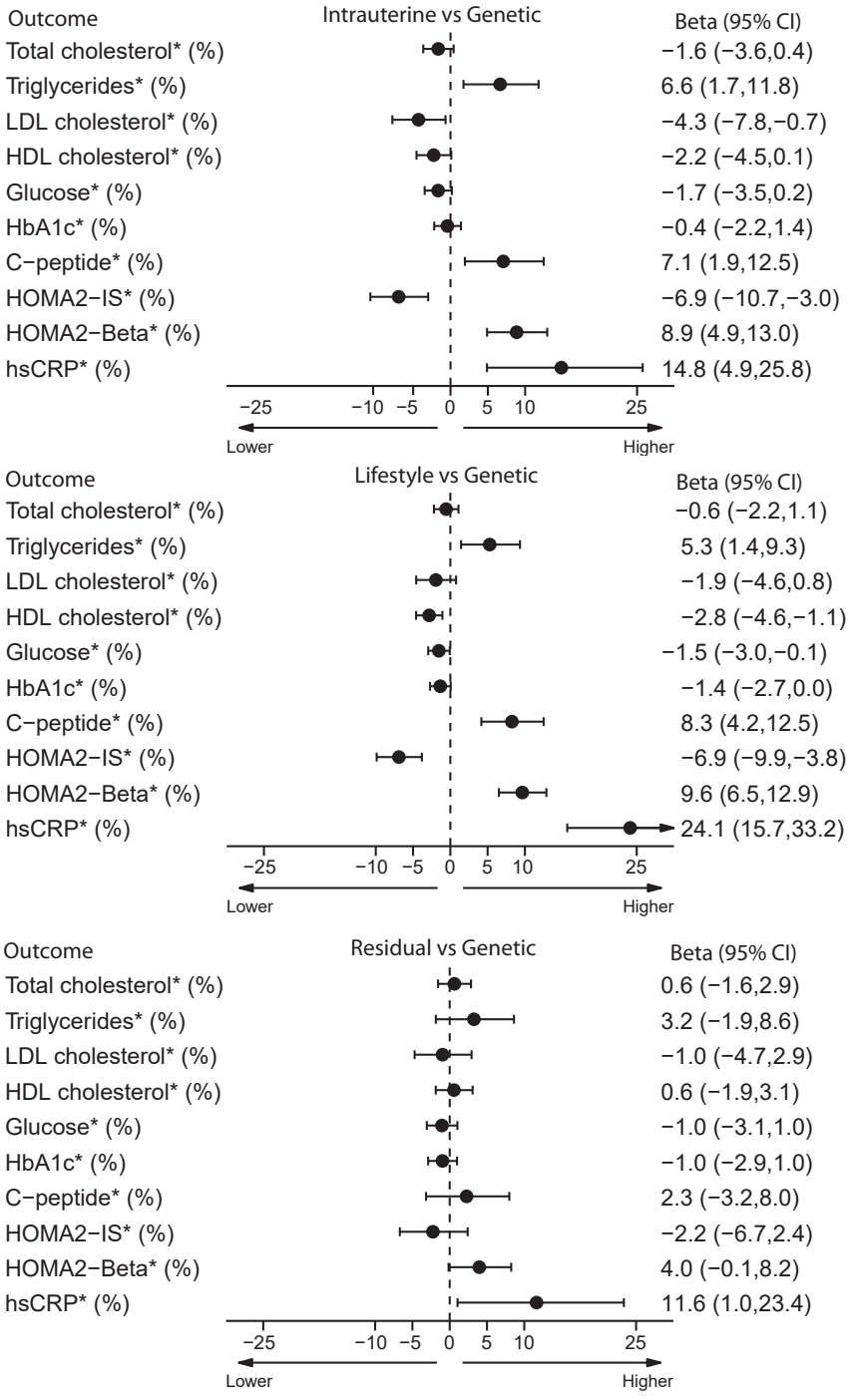

***Fig. 3*: Linear regression analysis of metabolic factors (subclinical inflammation, lipid, and glucose-insulin metabolism). Legend:** Linear regression analysis according to phenotype groupings, with the genetic group as reference. Points represent beta estimates and horizontal error bars represent 95% confidence intervals. Variables marked with * were log-transformed and beta estimates are therefore presented as percentage changes for interpretation. All models are adjusted for sex, calendar birth year, age at DD2 enrolment, diabetes duration, and genetic principal components. Abbreviations: CI = confidence interval; LDL = low-density lipoprotein; HDL = high-density lipoprotein; HbA1c = haemoglobin A1c; HOMA = Homeostasis Model Assessment; IS = insulin sensitivity; hsCRP = high-sensitivity C-reactive protein; DD2 = Danish Centre for Strategic Research in Type 2 Diabetes.

respectively) (Supplementary Table S5). The lifestyle group was more likely than the genetic group not to be treated with glucose-lowering medication (PR 1.26 [95% CI 1.07, 1.47]) (Supplementary Table S5). Further adjustments did not attenuate the findings (Supplementary Table S5). At enrolment, the intrauterine group, compared with the genetic group, had substantially greater likelihood of prior stroke (PR 1.78 [95% CI 1.21, 2.62]) and afib (PR 1.47 [95% CI 1.08, 2.01]). The prevalence was also increased for HF (PR 1.35 [95% CI 0.93, 1.97], MACE (PR 1.20 [95% CI 0.99, 1.47]), and CKD (PR 1.29 [95% CI 0.95, 1.75]), but decreased for neuropathy (PR 0.53 [95% CI 0.26, 1.08]) (Supplementary Table S5). The lifestyle group, compared with the genetic group, was more likely to have prevalent afib (PR 1.38 [95% CI 1.08, 1.75]) and CKD (PR 1.28 [95% CI 1.01, 1.62]) (Supplementary Table S5). Further explorative adjustments attenuated the elevated prevalence of MACE, stroke, and HF in the intrauterine group, whereas the associations for the lifestyle group persisted (Supplementary Table S5). Further adjustments generally lowered estimate precision (Supplementary Table S5).

Follow-up analyses

During a median follow-up of 10.1 years (IQR 7.0, 11.8 years), 1031 MACE (incidence rate 15.2 per 1000 person-years), 1838 microvascular diagnoses (incidence rate 31.4 per 1000 person-years), and 1340 deaths (incidence rate 18.4 per 1000 person-years) occurred (Supplementary Table S3). The 10-year standardised MACE risk was 14.8% (95% CI 12.7, 17.0) (intrauterine), 13.2% (95% CI 12.2, 14.3) (lifestyle), and 11.5% (95% CI 9.9, 13.3) (genetic), yielding an excess RD of +3.3% (95% CI 0.6, 6.0) with an adjusted (a)HR of 1.33 (95% CI 1.06, 1.66) for intrauterine, and RD +1.7% (95% CI −0.3, 3.6) with an aHR of 1.17 (95% CI 0.98, 1.39) for lifestyle, *vs.* genetic aetiologies (Fig. 4a, Fig. 5, Table 2). The 10-year standardised risk of microvascular complications was 25.9% (95% CI 23.2, 28.5) (intrauterine), 25.4% (95% CI 24.0, 26.7) (lifestyle), and 21.8% (95% CI 19.7, 24.1) (genetic), yielding an excess RD of +4.1% (95% CI 0.7, 7.5) with an aHR of 1.23 (95% CI 1.05, 1.45) for intrauterine, and RD +3.5% (95% CI 1.0, 6.1) with an aHR of 1.20 (95% CI 1.05, 1.37) for lifestyle, *vs.* genetic aetiologies (Figs. 4b and 5, Table 2). Ten-year standardised all-cause mortality was 16.4% (95% CI 14.3, 18.4) (intrauterine), 15.7% (95% CI 14.6, 16.7) (lifestyle), and 14.3% (95% CI 12.5, 17.3) (genetic), thus yielding a slightly higher RD of +2.0% (95% CI −0.5, 4.6) with an aHR of 1.17 (95% CI 0.96, 1.43) for intrauterine, and +1.3% (95% CI −0.6, 3.2) with an aHR 1.11 (95% CI 0.96, 1.29) for lifestyle, *vs.* genetic aetiologies (Figs. 4c and 5, Table 2); however, the risk estimates for all-cause mortality had limited precision. Further adjustments did not substantially change any associations (Supplementary Table S6).

For individual endpoints, compared to the genetic group, the intrauterine group had greater risk of stroke (aHR 1.46 [95% CI 1.06, 2.05]), HF (aHR 1.38 [95% CI 0.92, 2.07]), peripheral arterial disease (PAD) (aHR 2.20 [95% CI 1.26, 3.84]), death from CVD (aHR 1.68 [95% CI 1.06, 2.67]), CKD (aHR 1.21 [95% CI 1.01, 1.46]), and retinopathy (aHR 1.29 [95% CI 0.92, 1.81]) (Fig. 5), and the lifestyle group had greater risk of HF (aHR 1.37 [95% CI 1.00, 1.88]), MI (aHR 1.21 [95% CI 0.95, 1.55]), PAD (aHR 1.50 [95% CI 0.94, 2.41], death from CVD (aHR 1.48 [95% CI 1.03, 2.13]), and CKD (aHR 1.21 [95% CI 1.05, 1.40]) (Fig. 5). Further adjustments did not substantially change any associations (Supplementary Table S6).

Additional and sensitivity analyses

Additional adjustments for preterm status resulted in a 1.1-year (95% CI 0.1-, 2.0-year) older age at T2D diagnosis and attenuation of the elevated risk of microvascular complications in the intrauterine *vs.* genetic group (Supplementary Tables S7 and S9). Further adjustments for birthweight and BMI PGSs did not attenuate any other findings (Supplementary Tables S7–S9). Restricting the analysis to individuals without prevalent CVD generally yielded results consistent with those from the main analysis (Supplementary Table S10). However, the intrauterine group's associations with incident HF and retinopathy were attenuated, whereas the associations with death from CVD and all-cause mortality increased further (aHR 2.75 [95% CI 1.15, 6.60] and 1.30 [95% CI 1.00, 1.70], respectively) (Supplementary Table S10). In the lifestyle group, restricting analyses to CVD-naïve individuals further increased risk of MACE (aHR 1.40 [95% CI 1.08, 1.83]), MI (aHR 1.60 [95% CI 1.09, 2.34]), and death from CVD (aHR 2.35 [95% CI 1.11, 4.98]) (Supplementary Table S10).

Overall, the alternative median cut-off subgrouping yielded similar associations, generally characterised by larger but less precise effect estimates (Supplementary Tables S11–S17). Compared with the genetic group, the genetic/intrauterine group had a 4.5-year (95% CI 3.2-, 5.9-year) younger age at diagnosis, 1.5 kg/m^2 (95% CI 0.8, 2.3) lower BMI at enrolment, 1.3 kg/m^2 (95% CI 0.3, 2.3) lower BMI at 20 years of age, 2.9 cm (95% CI 1.4, 4.4) smaller waist circumference, and 2.9 mmHg (95% CI 0.6, 5.2) higher systolic blood pressure. In follow-up analyses, the genetic/intrauterine group had a greater 10-year standardised risk of microvascular complications (RD +6.0% [95% CI 0.7, 11.4]) and a lower risk of all-cause mortality (RD −3.6% [95% CI −7.6, 0.4]) than the genetic group, although estimates had limited precision. The genetic/intrauterine group also showed elevated aHRs for PAD (2.60 [95% CI 1.18, 5.75]), CKD (1.27 [95% CI 0.96, 1.69]), and retinopathy (1.62 [95% CI 1.01, 2.60]) (Supplementary Tables S16 and S17).

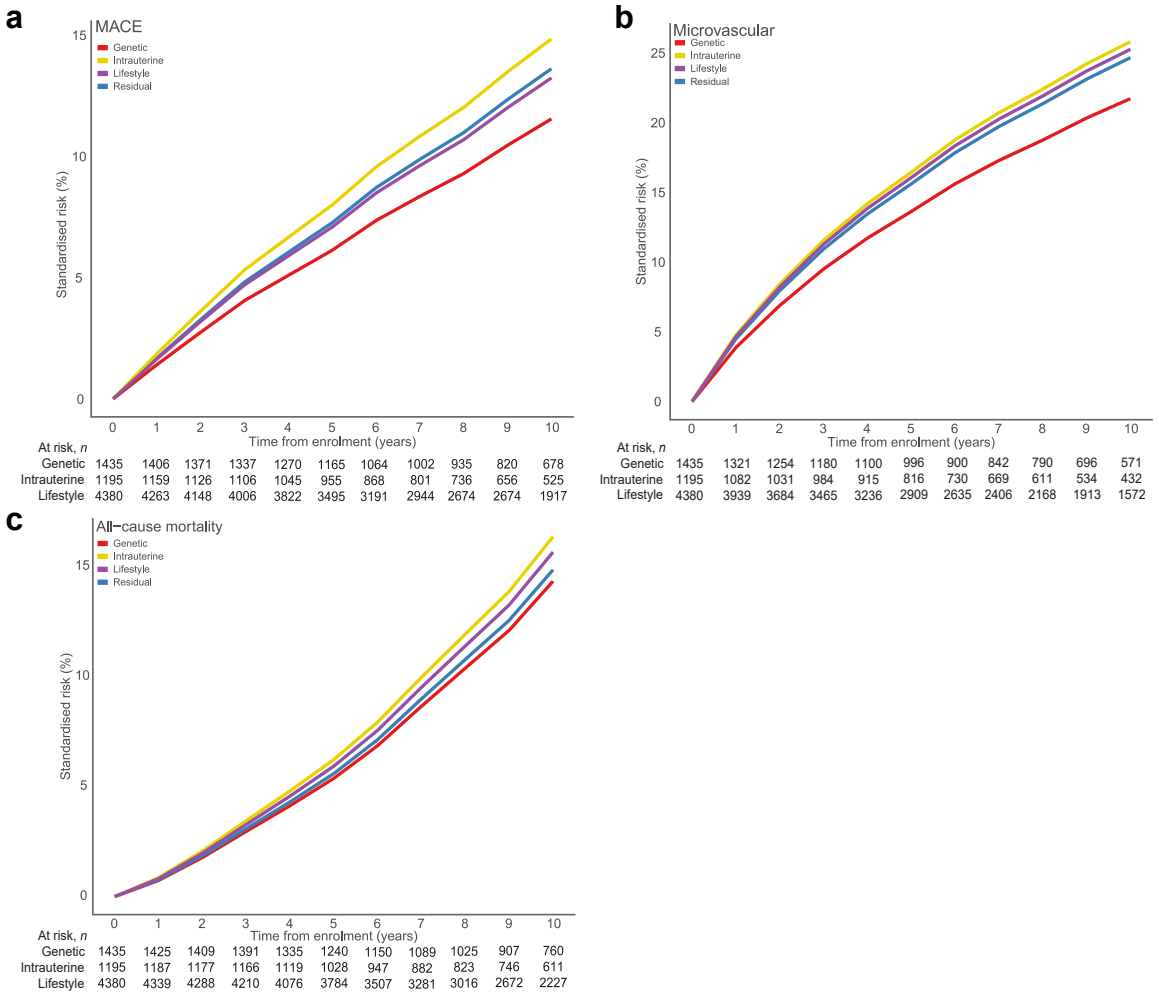

***Fig. 4:* Risk curves for complications according to phenotypes. Legend:** Standardised absolute risk curves for (a) MACE, (b) microvascular complications, and (c) all-cause mortality by phenotype. Curves were estimated using the parametric G-formula, based on cause-specific Cox regression models, and standardised to the distribution of sex, calendar birth year, age at DD2 enrolment, diabetes duration, and genetic principal components. Confidence bands are not shown to preserve readability; corresponding 10-year standardised risks and 95% confidence intervals are reported in the text and Table 2. Numbers below the x-axis indicate individuals at risk over follo-up. Abbreviations: MACE = major adverse cardiovascular events; DD2 = Danish Centre for Strategic Research in Type 2 Diabetes.

Using a T2D-specific PGS[22] instead of the GRS applied in the main analysis generally resulted in similar associations (Supplementary Tables S18–S21), although some differences emerged. The intrauterine group's associations with elevated risk of HF and death from CVD disappeared, as did the lifestyle group's associations with elevated risks of MACE, HF, PAD, death from CVD, and CKD (Supplementary Tables S20 and S21).

Exploratory sex-stratified analyses suggested some heterogeneity in the magnitude of the estimates. Macrovascular associations in the intrauterine and lifestyle groups tended to be more pronounced in men, whereas associations with microvascular complications in the lifestyle group appeared more pronounced in women; however, many sex-stratified estimates were imprecise (Supplementary Table S22).

Discussion

Using a T2D GRS and birthweight as proxies for etiological risk domains, we observed substantial differences in clinical presentation and disease progression among individuals with newly diagnosed T2D.

Compared with the genetic group, individuals in the intrauterine or lifestyle group presented with more pronounced insulin resistance, greater subclinical inflammation, and elevated risk of macro- and microvascular complications. The intrauterine group showed earlier age at T2D onset, whereas the lifestyle group had

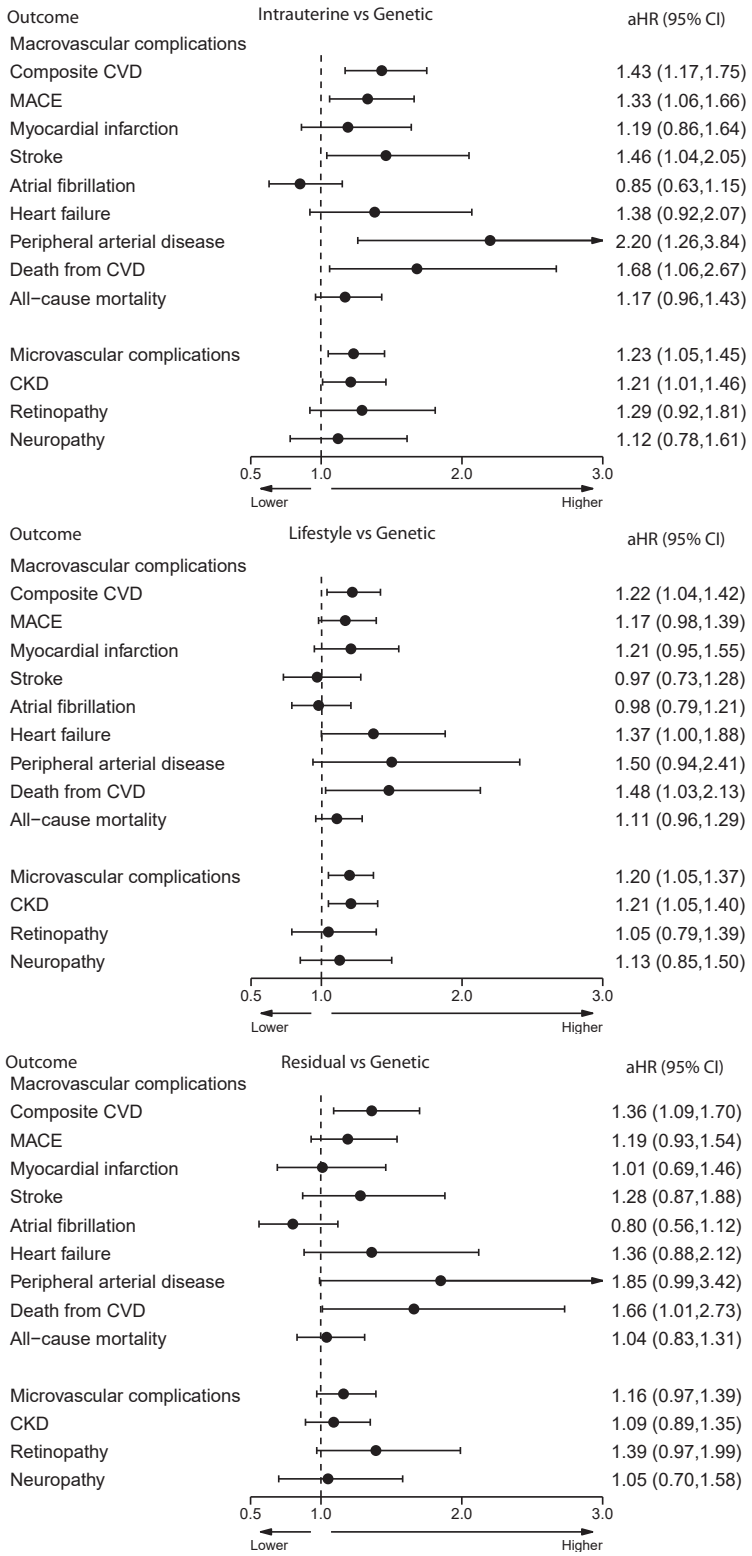

Fig. 5: **Hazard ratios of macrovascular and microvascular complications after type 2 diabetes diagnosis, according to phenotype groupings**. **Legend:** Hazard ratios according to phenotypes, with the genetic group as reference, estimated from cause-specific Cox regression

Complications	10-year standardised risk (95% CI)	Risk difference (95% CI)
MACE		
Genetic	11.5 (9.9, 13.3)	Ref
Intrauterine	14.8 (12.7, 17.0)	3.3 (0.6, 6.0)
Lifestyle	13.2 (12.2, 14.3)	1.7 (−0.3, 3.6)
Residual	13.6 (11.2, 16.1)	2.1 (−0.9, 5.1)
All-cause mortality		
Genetic	14.3 (12.7, 16.0)	Ref
Intrauterine	16.4 (14.3, 18.4)	2.0 (−0.5, 4.6)
Lifestyle	15.7 (14.6, 16.7)	1.3 (−0.6, 3.2)
Residual	14.9 (12.5, 17.3)	0.5 (−2.3, 3.4)
Microvascular		
Genetic	21.8 (19.7, 24.1)	Ref
Intrauterine	25.9 (23.2, 28.5)	4.1 (0.7, 7.5)
Lifestyle	25.4 (24.0, 26.7)	3.5 (1.0, 6.1)
Residual	24.8 (21.8, 27.9)	2.9 (−0.8, 6.7)

Legend: The 10-year risk estimates were derived using the parametric G-formula, based on cause-specific Cox regression models, and standardised to the distribution of sex, calendar year at birth, age at DD2 enrolment, diabetes duration, and genetic principal components. Abbreviations: MACE = major adverse cardiovascular events, CI = confidence intervals.

Table 2: **Ten-year standardised risk measures of complications according to phenotypes.**

later onset, higher BMI, and waist circumference. Absolute complication risks were numerically highest in the intrauterine group.

Studies have shown associations between LBW and T2D severity, indicated by younger age at diagnosis and elevated risks of CVD and CKD,[7,23–25] while genetic susceptibility has been associated with primarily disease onset rather than prognosis.[26,27] Our findings extend this evidence by demonstrating that a predominant adverse intrauterine and lifestyle-related aetiology is associated with a more severe disease course than a predominant genetic aetiology. This is further supported by a recent meta-analysis indicating that GWAS-derived T2D PGS are strongly associated with disease onset but have near–null associations with disease specific mortality among affected individuals.[27] Thus, prenatal, or lifestyle-related pathways to T2D appear more strongly associated with a more severe disease course in T2D than genetic T2D susceptibility.

The elevated complications risk associated with LBW might be due to generalised impaired foetal development and multi-organ immaturity,[5,28] rather than glycaemic mechanisms alone. Indeed, LBW is associated with T2D comorbidities including hypertension, CVD, and CKD, even in people without diabetes.[5,28,29]

The lifestyle group was defined indirectly by exclusion of the highest genetic and intrauterine predisposition rather than by direct measurement of cumulative lifestyle exposure. Nevertheless, its higher adiposity at T2D onset and recalled at 20 years of age, as well as less favourable health behaviours, supporting construct validity. Adjustment for BMI attenuated cross-sectional metabolic differences but did not substantially reduce long-term complications risk. The reasons underlying this observation remain unclear but might reflect the incompleteness of BMI as a marker of body mass distribution, and/or of lifelong adverse lifestyle patterns. Alternatively, it may reflect diminished compliance with recommended lifestyle interventions than observed in groups with predominantly genetic or intrauterine predispositions. The alternative subgrouping approach, defined by more extreme cut-offs to enrich the presumed predominant aetiological domains, yielded broadly similar patterns, although the effect sizes generally increased with diminished precision. The markedly lower age at diagnosis and BMI in the combined genetic/intrauterine group further suggest that these domains are not mutually exclusive and may act additively, consistent with a greater burden of microvascular complications. In that perspective, the lower all-cause mortality in this subgroup should be interpreted cautiously due to low statistical power. Notably, because inclusion required survival until both T2D diagnosis and DD2 enrolment. As a result, survivor selection may have excluded individuals with the most severe combined genetic and intrauterine risk burden.

The foetal insulin hypothesis suggests genetic confounding in the LBW-T2D association, owing to insulin-related genetic variants affecting foetal growth.[30]

models. Points represent adjusted hazard ratio estimates and horizontal error bars represent 95% confidence intervals. All models are adjusted for sex, calendar birth year, age at DD2 enrolment, diabetes duration, and genetic principal components. Abbreviations: aHR = adjusted hazard ratio; CI = confidence interval; MACE = major adverse cardiovascular event; CVD = cardiovascular disease; CKD = chronic kidney disease.

However, our findings indicate that LBW reflects developmental pathways not adequately explained by currently known genetic variants, as individuals with severe disease trajectories had predominant intrauterine rather than genetic predispositions.

The genetic group had the most severely reduced insulin secretion, in agreement with genetic T2D susceptibility variants affecting insulin secretion.[31] In contrast, intrauterine and lifestyle predispositions appear to mediate T2D risk via differential effects on liver, adipose tissue, and muscle insulin action.[5] Differences in insulin secretion and action also might partly explain variations in medication use at diagnosis. Specifically, the genetic group used more glucose-lowering medications likely to compensate for impaired insulin secretion, whereas the more insulin resistant intrauterine and lifestyle groups had greater antihypertensive medication use, possibly reflecting the link between insulin resistance and hypertension.[32] Compared with the genetic group, the intrauterine and lifestyle groups were further characterised by greater subclinical inflammation and dyslipidaemia, thus potentially contributing to the observed increased complication risk.

Adjustment for prematurity attenuated some associations. However, interpretation warrants caution because LBW is among markers used by midwives to judge newborns' prematurity.[7] Hence, LBW and prematurity are both reflecting consequences of adverse pregnancy events and have approximately same increased risk estimates of immediate after birth as well as later in life adverse health outcomes.[4] To take account of this important dimension, it has been proposed to use the collective term 'small vulnerable newborns' for these two categories.[4] Adjusting birthweight for preterm status most likely therefore represent an overadjustment.

Strengths of this study include its well-characterised nationwide cohort of recently diagnosed individuals with T2D, recruited from general practice and outpatient hospital clinics, with prospective follow-up for 10 years after diagnosis.

Several limitations merit consideration. First, proxies for genetic predisposition and adverse intrauterine environment might not fully capture genetic predisposition or accurately differentiate between non-genetic factors influencing foetal growth. Although results remained robust after adjustment for birthweight and BMI PGS, undiscovered genetic variants affecting birthweight or T2D risk cannot be excluded. Sex-stratified analyses suggested some heterogeneity in associations, although estimates were imprecise. Because birthweight cut-offs were defined in the overall cohort rather than sex-specific distributions, the lowest birthweight quartile may have captured different relative degrees of intrauterine adversity in women and men. The lifestyle group, defined indirectly by exclusion, may be the least precisely defined group. However, its higher adiposity and less favourable health behaviours support construct validity. Because individuals are likely to carry risk across multiple aetiological domains and the groups were defined using pragmatic proxy-based cut-offs, misclassification is inevitable and the framework should not be interpreted as assigning individuals to pure causal categories. Second, the cross-sectional assessment at T2D diagnosis is subject to survivor bias, as individuals with adverse early-life exposures who died or developed severe disease before diagnosis are not represented. Third, complications identified from hospital diagnosis are incompletely captured, particularly for microvascular outcomes. However, completeness for CKD is improved through linkage to laboratory measurements.[33] Although the cohort was large overall, some subgroup and endpoint-specific analyses had limited sample size and precision, particularly for less frequent outcomes and exploratory analyses. Because multiple outcomes were examined, some findings may reflect chance and should be interpreted cautiously, particularly in the exploratory and sensitivity analyses.

Finally, many individuals had initiated cardiometabolic treatments before enrolment, and information on post-diagnosis lifestyle and treatment changes was unavailable. Because DD2 is based on clinical diagnosis in routine care, some misclassification of diabetes type cannot be excluded. We also lacked information on education, income, and maternal/paternal risk factors associated with T2D. In addition, the final analytic sample was a selected subset of DD2 with available genotyping and historical birthweight data, obtained in a predominantly Scandinavian, European-ancestry population within a Danish universal healthcare setting, and may therefore not generalise directly to populations with different genetic origins, early-life exposures, lifestyle patterns, or healthcare systems. Future studies are therefore needed to validate this framework in more diverse populations. Unfortunately, we are unaware of other current suitable high quality validation cohorts of newly diagnosed T2D patients including both original objective birthweight and genetic data.

Individuals with predominantly intrauterine or lifestyle compared with genetic aetiologies had less favourable clinical phenotypes regarding metabolic factors at T2D diagnosis, and consistently higher subsequent risk of both macrovascular and microvascular complications. Further studies are needed to understand the extent to which the applied proxies, in combination with other clinical or biomarker variables, might improve risk prediction and guide treatment of T2D patients.

Contributors

AV and ALH conceived and designed the study. AV is the guarantor of the study. ALH performed the statistical analysis and prepared the first draft of the manuscript. ALH, CB, LME, MKA, JSN, PV, KH, MHO,

HTS, RWT, and AV contributed to the interpretation of data and critically revised the content of the draft. AV and RWT supervised the study. ALH and RWT have accessed and verified the data. All authors read and provided final approval of the version to be published; as such, they had full access to all data in the study and took responsibility for the integrity of the data and the accuracy of the data analyses.

Data sharing statement

Danish data protection legislation does not allow the authors to share the individual-level patient data and due to protected servers, software code will also not be made available. However, the Danish health registry data accessed for this study are available to researchers at authorised research institutions after application to the Danish Health Data Authority (by e-mail to forskerservice@sundhedsdata.dk). Requests to use data from the DD2 cohort can be made on the DD2 website, https://dd2.dk/forskning/ansoeg-om-data.

Declaration of interests

All authors have read and approved the manuscript. CB own stock in Novo Nordisk. MHO has received payments or honoraria for lectures, presentations, or educational events from AstraZeneca, Novo Nordisk A/S, Bohringer-Ingelheim A/S, Johnson & Johnson, and Teva A/S, and has an unpaid position as Chair of the Danish Hypertension Society and is a member of the Danish Research Council for Health. MHO has been supported by AstraZeneca A/S for the European Society of Cardiology 2025. The Department of Clinical Epidemiology, Aarhus University, and Novo Nordisk Foundation Center for Basic Metabolic Research receive funding for other studies in the form of institutional research grants to (and administered by) Aarhus University and University of Copenhagen, respectively. HTS has made paid evaluations for University of Oslo, Karolinska Institute, the Independent Research Fund Denmark, and the European Research Council. RWT has given presentations with or without financial compensation for AstraZeneca, Bayer, Bohringer-Ingelheim, Eli Liliy, Novo Nordisk, and Sanofi. JSN is employed by Sanofi A/S, Denmark. None of these studies have any relation to the present study. ALH, LME, MKA, PV, KH, and AV declares no competing interests.

Acknowledgements

We are grateful to all participants in the DD2 study and to the healthcare personnel who recruited them at general practices and outpatient clinics. We sincerely thank the DD2 management and the DD2 data managers. The DD2 study is supported by the Danish Agency for Science (grant numbers 09-067009 and 09-075724), the Danish Health and Medicines Authority, the Danish Diabetes Association, the Region of Southern Denmark, and the Novo Nordisk Foundation (grant numbers NNF17SA0030962-2, NNF20O0063292, and NNF17SA0030364). Project partners are listed on www.dd2.dk website. This work also was supported by a grant from the Novo Nordisk Foundation (NNF23SA0084103) and partly funded by the Swedish Research Council (EXODIAB, 2009-1039; 2018-02837). The Swedish ALF (Avtal om läkarutbildning och forskning) for Region Skåne, the Crafoord Foundation, and the Swedish Diabetes Association.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.104029.

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