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RESEARCH ARTICLE

Early-onset type 2 diabetes: Age gradient in clinical and behavioural risk factors in 5115 persons with newly diagnosed type 2 diabetes—Results from the DD2 study

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Abstract

Aim: To examine the association between early onset of type 2 diabetes mellitus (DM) and clinical and behavioural risk factors for later complications of diabetes.

Methods: We conducted a cross-sectional study of 5115 persons with incident type 2 DM enrolled during 2010-2015 in the Danish Centre for Strategic Research in Type 2 Diabetes-cohort. We compared risk factors at time of diagnosis among those diagnosed at ≤45 years (early onset) with diagnosis age 46 to 55, 56 to 65 (average onset = reference), 66 to 75, and >75 years (late onset). Prevalence ratios (PRs) were computed by using Poisson regression.

Results: Poor glucose control, ie, HbA1c ≥ 75 mmol/mol (≥9.0%) in the early-, average-, and late-onset groups was observed in 12%, 7%, and 1%, respectively (PR 1.70 [95% confidence intervals (CI) 1.27, 2.28] and PR 0.17 [95% CI 0.06, 0.45]). A similar age gradient was observed for severe obesity (body mass index > 40 kg/m^2: 19% vs. 8% vs. 2%; PR 2.41 [95% CI 1.83, 3.18] and 0.21 (95% CI 0.08, 0.57]), dyslipidemia (90% vs. 79% vs. 68%; PR 1.14 [95% CI 1.10, 1.19] and 0.86 [95% CI 0.79, 0.93]), and low-grade inflammation (C-reactive protein > 3.0 mg/L: 53% vs. 38% vs. 26%; PR 1.41 [95% CI 1.12, 1.78] and 0.68 [95% CI 0.42, 1.11]). Daily smoking was more frequent and meeting physical activity recommendations less likely in persons with early-onset type 2 DM.

Conclusions: We found a clear age gradient, with increasing prevalence of clinical and behavioural risk factors the younger the onset age of type 2 DM. Younger persons with early-onset type 2 DM need clinical awareness and support.

KEYWORDS

cross sections study, DD2 study, early onset type 2 diabetes, health behaviour, risk factors

1 | INTRODUCTION

The rising global burden of type 2 diabetes mellitus (DM) in middle-aged and older persons is now accompanied by increasing prevalence in youth and younger adults.[1-5] This is alarming because early-onset

An abstract with similar but less detailed analysis has been presented with a poster at the European Association for the Study of Diabetes (EASD) 2016: Bo, A et al. High burden of cardiovascular risk factors and poor glycemic control in type 2 diabetes patients diagnosed before the age of 45 years in Denmark: results from the Danish Center for Strategic research in Type 2 Diabetes (DD2) study. 52nd EASD Annual Meeting, Munich, 12-16 September 2016.

type 2 DM (onset age < 40 or 45 years) is likely to be associated with increased risk of complications later in life. Epidemiological studies have shown increased rates of retinopathy, nephropathy, cardiovascular disease, and premature mortality among persons with early-onset type 2 DM, compared with persons with later-onset type 2 DM.[6-11] The excess burden of late complications is likely related to longer disease duration during the life course among early-onset cases but may also be due to higher prevalence of risk factors at the time of type 2 DM onset.[12] Cross-sectional studies have reported a higher prevalence of poor glucose control, obesity, hypertension, increased low-density lipoprotein (LDL), and of family history of type 2 diabetes among persons with early-onset type 2 DM compared with later-onset individuals at different duration of type 2 DM.[13-19] The few studies of behavioural risk factors in persons with early- vs. later-onset type 2 DM have reported a higher smoking prevalence and lower physical activity level among early-onset individuals.[16,20] Former studies primarily used a dichotomization of "early" (at <40 or 45 years of age) versus "late" onset (at >40 or 45 years of age). This may hide possible age differences in presence of clinical and behavioural risk factors, which can be crucial for providing the appropriate health services to persons newly diagnosed with type 2 DM.

In the present study, we obtained information at time of diagnosis for a large cohort of persons clinically diagnosed with type 2 DM. We hypothesized that persons with early-onset type 2 DM have a high burden of clinical and behavioural risk factors for later complications. We aimed to explore whether there is a gradient in the association between age at type 2 DM diagnosis and prevalence of these risk factors.

2 | METHODS

2.1 | Study design and study population

In a cross-sectional study based on a cohort of persons newly diagnosed with type 2 DM, we compared clinical and behavioural risk factors among persons diagnosed at age ≤ 45 years (early onset) and those diagnosed at ages 46 to 55 years, 56 to 65 years (average onset = reference group), 66 to 75 years, and >75 years (late onset). A total of 7053 participants were enrolled consecutively from general practices and hospital outpatient clinics between January 2010 and June 2015 as part of a nationwide cohort established by the Danish Center for Strategic research in Type 2 Diabetes (DD2).[21] Of these participants, we were able to include 5115 patients who could currently be linked to other databases for a detailed assessment of risk factors (see below).

2.2 | Data collection

Enrolment in the DD2 cohort has previously been described by Nielsen et al.[21] In brief, patients are diagnosed with type 2 DM in everyday routine clinical practice—either by hospital physicians or general practitioners—and are thereafter invited to participate in the DD2 project. In both settings, the diagnostic criteria have followed Danish national guidelines and World Health Organization criteria throughout the study period. If a patient gives informed consent to participate, the physician may choose to perform the DD2 enrolment procedures himself or may refer the patient to a hospital outpatient clinic, where all procedures are performed. Upon enrolment, an online registration form[21] containing patient-reported and clinical examination data is completed. Fasting urine and blood samples are obtained and then stored in the DD2 biobank.

The unique Central Personal Registration number provided to all Danish residents at birth or upon immigration is used to link DD2 data with Danish national health registries. In our study, these included (1) the Danish National Prescription Registry, containing individual-level information on prescriptions dispensed from all Danish community pharmacies; (2) the Danish National Patient Registry, containing information on hospital inpatient and outpatient clinic contacts; and (3) the Danish Diabetes Database for Adults (DDDA), a nationwide quality-of-care database containing indicators for adults with diabetes reported from general practices and hospital outpatient clinics.[22] Supplementary data sources in the DD2 have been described by Thomsen et al.[22]

Fasting glucose was measured as a part of the enrolment procedure. Information on HbA1c was collected from the DDDA, using the HbA1c value measured closest to the DD2 enrolment date. The chosen cut point for increased LDL cholesterol at 2.5 mmol/L is the Danish recommended threshold for initiating lipid-lowering treatment.[23] We defined the presence of any dyslipidemia according to the American Diabetes Association[24]: LDL cholesterol >2.60 mmol/L, or HDL cholesterol <1.02 mmol/L, or triglyceride >1.7 mmol/L. C-reactive protein (CRP) was available for a biobank subgroup of the first consecutive 1037 patients enrolled in the DD2 project. Glutamic Acid Decarboxylase (GAD) antibody was measured after enrolment, based on biobank samples. Data on behavioural risk factors at enrolment included physical activity, alcohol consumption, and smoking. Information on physical activity and alcohol consumption was self-reported. The assessment of physical activity level was based on number of days with at least 30 minutes of moderate to hard physical activity. High-risk alcohol consumption was categorized according to the Danish Health Authority's definitions as more than 21 and 14 drinks weekly for men and women, respectively. Information on smoking was obtained from the DDDA, and information on medications at enrolment was obtained from the Danish National Prescription Registry.

2.3 | Ethics

Participants in the DD2 project signed a written informed consent document, after receiving information approved by the Danish National Committee on Health Research Ethics. Patient registration and biospecimen collection for the DD2 project were approved by the Danish National Committee on Health Research Ethics (record number S-20100082) and the Danish Data Protection Agency (record number 2008-58-0035).

2.4 | Statistical analysis

Prevalence proportions were estimated for categorical variables. Medians with interquartile ranges were calculated for continuous variables, as data were not normally distributed. To compare prevalence in different age groups, prevalence ratios (PRs) with 95%

confidence intervals (95% CIs) were calculated by using Poisson regression analysis. The average-onset group (diagnosis at age 56-65 years) was used as the reference group. For many patients, the first prescription of a glucose lowering drug (GLD) had been made several months before enrolment into the DD2 cohort. Moreover, the treatment duration before enrolment varied across age groups (Table 4), and therefore could be considered a possible confounder for parameters affected by GLDs. For this reason, we adjusted the PRs of body mass index (BMI), central obesity, HbA1c, and fasting plasma glucose for time elapsed between first dispensed prescription of a GLD and enrolment in the DD2 cohort. We refrained from using further multivariate adjustment models, because most of the risk factors we examined may act as intermediates and clusters in the same causal pathophysiological pathways and are impossible to disentangle in a cross-sectional design. All analyses were performed by using SAS version 9.2 (SAS institute, Inc., Cary, North Carolina).

3 | RESULTS

3.1 | Background characteristics

Median age in the study cohort was 62.2 years (interquartile range: 53.3-68.8 years), and 10% were diagnosed at age ≤ 45 years (early onset). The proportion of women was approximately 40% in the <45, 46 to 55, and 66 to 75 year age groups and 49% in the late-onset (>75 years) group (Table 1). Family history of type 2 DM was clearly highest in the early-onset group (64%), decreasing to 52% in the average-onset group, and to 40% in the late-onset group. The prevalence of previous gestational diabetes mellitus was 22% among women in the early-onset group—much higher than in the other groups. A positive test for GAD antibodies was present in 7% in the early-onset group, and in less than 3% in the age groups above 46 years (PR for early onset vs. average onset 2.60 [95% CI 1.66; 4.08]) (Table 1). While positive GAD antibodies in retrospect indicates autoimmune diabetes, we kept these few patients in our cohort for reasons of completeness and generalizability for everyday clinical practice-diagnosed type 2 DM (when re-running all analysis while excluding GAD positive patients, all results only changed marginally [data not shown]).

3.2 | Glucose control

We observed a clear gradient of increasingly poor glucose control in members of the younger-onset groups, after adjusting for duration of glucose-lowering treatment before enrolment (Table 1 and Figures 1A and 1B). For example, the prevalence of poor control, ie, HbA1c ≥75 mmol/mol (≥9.0%) in the early-, average-, and late-onset groups, was observed in 12%, 7%, and 1%, respectively (PR 1.70 [95% CI 1.27, 2.28] and PR 0.17 [95% CI 0.06, 0.45]) (Table 1). A reverse gradient that was found for good glucose control, ie, HbA1c 48 to 53 mmol/mol (6.5%-7.0%) in the early-, average-, and late-onset groups, was observed in 20%, 27%, and 35%, respectively (PR 0.73 [95% CI 0.60, 0.89] and PR 1.28 [95% CI 1.08, 1.51]) (Table 1). A similar age gradient, with higher glucose levels in younger age groups, was observed for fasting plasma glucose (Figure 1B).

3.3 | Other clinical risk factors

In the early-onset group, 39% had BMI >35, 9 in 10 had central obesity (88%), one third had hypertension (32%), and close to half had a LDL >2.5 mmol/L (50%) and CRP >3.0 mg/L (53%) (Table 2). For risk factors such as high BMI, LDL, and CRP, there was a clear gradient of higher prevalence with earlier age of onset (Figures 1C and 1E). For example, the gradient for BMI >40 was 19% (early onset), 8% (average onset), and 2% (late onset) (PR 2.41 [95% CI 1.83, 3.18] and 0.21 [95% CI 0.08, 0.57]). The gradient for dyslipidemia was 90% vs. 79% vs. 68% for the three groups (PR 1.14 [95% CI 1.10, 1.19] and 0.86 [95% CI 0.79, 0.93]), and for CRP >3.0 mg/L, this was 53%, 38%, and 26% (PR 1.41 [95% CI 1.12, 1.78] and 0.68 [95% CI 0.42, 1.11]) (Table 2). The prevalence of hospital-diagnosed retinopathy was also higher in the early-onset group (7%) than in the average-onset group (5%) (PR 1.58 [95% CI 1.08, 2.31]). Albuminuria was present in close to one in five persons in the four youngest onset groups and still higher in the late-onset group (28%) (PR for onset >75 years vs. 56-65 years: 1.44 [95% CI 1.18, 1.76]). Hypertension was present in about one third of persons in all five age-of-onset groups (Table 2 and Figure 1D).

3.4 | Behavioural risk factors

The prevalence of performing at least 30 minutes of moderate to intensive physical activity/day was 22% in the early-onset group, increasing with age to 32% in the average-onset group (PR for early vs. average onset: 0.69 [95% CI 0.58, 0.82]), peaking at 36% among 66 to 75 year olds (PR for the 66-75 years-group vs. average-onset group: 1.12 [95% CI 1.02, 1.23]) (Table 3 and Figure 1F). There was also a gradient in prevalence of daily smoking; 24%, 20%, and 8% in the early-, average-, and late-onset groups, respectively (PR 1.18 [95% CI 0.98, 1.42] and PR 0.39 [95% CI 0.27, 0.56]) (Table 3 and Figure 1F). Self-reported high-risk alcohol intake was below 10% in all age groups and lower in the early-onset (4%) than in the average-onset (7%) group (PR 0.50 [95% CI 0.31, 0.81]) (Table 3).

3.5 | Therapy

Between 75% and 80% of persons in the five age-of-onset groups received noninsulin GLDs at time of cohort enrolment (Table 4). The prevalence of using no GLDs was lowest in the early-onset group (8%) and increased to 15% and 22% in the average- and late-onset groups, respectively (PR for early onset 0.56 [95% CI 0.41, 0.76] and for late onset 1.47 [95% CI 1.18, 1.84]). In contrast, the use of both insulin and noninsulin drugs was highest in the early-onset group (11%) and decreased to 6% and 2% in the average- and late-onset groups. (PR 1.78 [95% CI 1.30, 2.45] and PR 0.39 [95% CI 0.20, 0.77]) (Table 4 and Figure 1G). Insulin use was higher (21%) among GAD antibody positive cohort members than among the GAD antibody negative members (7%), but the finding of higher insulin use in the early-onset group remained when excluding GAD antibody positive individuals (data not shown). In the early-onset group, 40% received antihypertensive drugs, 53% received lipid-lowering drugs, and 8% received anticoagulation drugs. Use of all three drug types increased with age of onset (Figure 1H).

TABLE 1 Background characteristics and glucose control among 5115 persons with newly diagnosed type 2 diabetes in 5 groups defined by age at diagnosis

		Age at Diagnosis				
Background Characteristics	**Missing N**	**≤45 years n = 516**	**46-55 years n = 1091**	**56-65 years n = 1651**	**66-75 years n = 1466**	**>75 years n = 391**
Female, %	0	42.2	39.5	42.0	40.9	48.6
PR (95% CI)		1.01 (0.90-1.13)	0.94 (0.86-1.03)	1 (ref)	0.97 (0.90-1.06)	1.16 (1.03-1.30)
Family history of T2DM [I],%	0	63.6	61.8	51.9	46.0	40.2
PR (95% CI)		1.23 (1.13-1.33)	1.19 (1.11-1.27)	1 (ref)	0.89 (0.83-0.95)	0.77 (0.68-0.88)
Previous gestational diabetes[II], %	0	21.6	3.7	0.1	-	-
GAD-positive[III], %	270	6.8	3.0	2.6	2.3	0.3
PR (95% CI)		2.60 (1.66-4.08)	1.14 (0.72-1.81)	1 (ref)	0.87 (0.55-1.38)	0.10 (0.01-0.74)
Enrolment performed in hospital outpatient clinic, %	0	64.1	56.7	51.2	40.9	28.9
Enrolment performed in general practice, %	0	35.9	43.3	48.8	59.1	71.1
Glucose Control						
HbA1c, mmol/mol, m (IQR)*	83	6.8 (6.2-8.0)	6.7 (6.2-7.4)	6.6 (6.1-7.2)	6.4 (6.1-6.9)	6.5 (6.1-6.9)
<48 (<6.5%), %		35.5	40.0	43.9	50.1	48.4
PR (95% CI)		0.85 (0.74-0.97)	0.93 (0.85-1.03)	1 (ref)	1.14 (1.05-1.24)	1.15 (1.01-1.31)
48-53 (6.5-7%), %		20.4	24.8	26.7	29.3	34.8
PR (95% CI)		0.73 (0.60-0.89)	0.90 (0.79-1.03)	1 (ref)	1.11 (0.99-1.24)	1.28 (1.08-1.51)
53-58 (7.0-7.5%), %		12.0	11.9	11.7	9.1	11.8
PR (95% CI)		0.99 (0.76-1.3)	1.02 (0.82-1.25)	1 (ref)	0.80 (0.65-0.99)	0.97 (0.70-1.33)
58-75 (7.5-9.0%), %		19.8	13.9	10.8	9.1	3.9
PR (95% CI)		1.75 (1.40-2.19)	1.26 (1.02-1.54)	1 (ref)	0.86 (0.70-1.07)	0.38 (0.23-0.64)
≥75 (≥9.0%), %		12.4	9.3	6.8	2.4	1.0
PR (95% CI)		1.70 (1.27-2.28)	1.33 (1.03-1.73)	1 (ref)	0.37 (0.25-0.54)	0.17 (0.06-0.45)
Fasting blood glucose, mmol/L*	637	7.6 (6.5-9.2)	7.4 (6.5-8.7)	7.2 (6.4-8.3)	7.0 (6.3-7.9)	6.8 (6.2-7.7)
<6.5, %		25.1	25.7	28.3	31.8	38.3
PR (95% CI)		0.88 (0.73-1.06)	0.92 (0.79-1.06)	1 (ref)	1.12 (0.98-1.26)	1.43 (1.21-1.70)
6.5-7.0, %		11.5	14.5	16.8	19.1	18.7
PR (95% CI)		0.73 (0.54-0.97)	0.90 (0.73-1.10)	1 (ref)	1.20 (1.01-1.43)	1.23 (0.95-1.60)
7.0-7.5, %		11.8	13.2	14.3	14.3	15.4
PR (95% CI)		0.82 (0.61-1.10)	0.93 (0.74-1.15)	1 (ref)	1.02 (0.84-1.23)	1.02 (0.75-1.38)
7.5-9.0, %		24.2	25.7	24.6	23.0	21.2
PR (95% CI)		0.96 (0.80-1.17)	1.01 (0.87-1.16)	1 (ref)	0.93 (0.81-1.07)	0.81 (0.64-1.03)
≥9.0, %		27.4	20.9	16.1	11.8	6.4
PR (95% CI)		1.65 (1.36-2.00)	1.28 (1.08-1.52)	1 (ref)	0.73 (0.60-0.88)	0.41 (0.27-0.62)

Estimates shown as percentages (%), medians (m) with interquartile ranges (IQR), or prevalence ratios (PR) with 95% confidence Intervals (95% CI).

*Adjusted for time since commencement of glucose-lowering treatment to enrolment in the DD2 cohort.

[I]Cohort member reported a father, mother, or child with type 2 diabetes.

[II]Estimates are given only as percentage of women.

[III]Glutamic Acid Decarboxylase antibody levels >30 kU/l.

4 | DISCUSSION

The key finding in this study was an age gradient of increasingly higher prevalence of most clinical and behavioural risk factors with younger age at type 2 DM diagnosis. Persons with early-onset type 2 DM had a markedly higher prevalence of severe obesity, dyslipidemia, low-grade inflammation, tobacco smoking, and physical inactivity. Importantly, persons in the early-onset group also had poorer glucose control than persons in the later-onset groups, although the early-onset individuals were more likely to receive both insulin and noninsulin glucose lowering treatment. Retinopathy and microalbuminuria were present at worrisome levels among persons with early-onset type 2 DM in light of their short disease duration and young age.

Previous studies corroborate clustering of risk factors in persons with newly diagnosed early-onset type 2 DM. A US study[18] found a higher mean BMI [39 kg/m^2 vs. 33 kg/m^2, P < .001] and higher mean HbA1c level (61 mmol/mol [7.7%] vs. 58 mmol/mol [7.5%], P = .030) in persons aged <45 years at diagnosis compared with those >45 years, and the study found equally high prevalence of abnormal lipids [82% vs. 78%, P = .130] in the 2 groups. A UK study[25] reported a mean BMI of 33 kg/m^2 and identified 80% with HbA1c >53 mmol/mol

FIGURE 1 Prevalence of risk factors for diabetes related complications among 5115 people with newly diagnosed type 2 diabetes in 5 groups defined by age at diagnosis

(7%) and 37% with hypertension among persons aged <40 years with newly diagnosed type 2 DM. Studies of persons with longer disease durations also found a worse risk factor profile among persons with early-onset type 2 DM than among later-onset individuals.[2,16] A large10-year follow-up study showed that that younger age is associated with greater increase in HbA1c after type 2 DM diagnosis,[26] and other studies found that persons with early-onset type 2 DM more often progress to using insulin, but remain more poorly controlled, than persons with later-onset type 2 DM.[7,16,17] A recent DD2 study found that young age was associated with a 1.3-fold

TABLE 2 Clinical risk factors among 5115 persons with newly diagnosed type 2 diabetes in 5 groups defined by age at diagnosis

		Age at Diagnosis				
Clinical Risk Factors	Missing N	≤45 years n = 516	46-55 years n = 1091	56-65 years n = 1651	66-75 years n = 1466	>75 years n = 391
Body mass index, kg/m^2, m (IQR)*	1280	32.7 (28.7-37.8)	31.7 (27.9-35.9)	30.8 (27.1-34.5)	29.4 (26.3-32.9)	28.4 (25.5-31.2)
BMI <25, %		6.9	9.9	13.4	15.8	20.3
PR (95% CI)		0.53 (0.36-0.77)	0.71 (0.55-0.92)	1 (ref)	1.19 (0.96-1.46)	1.48 (1.09-2.00)
BMI 25-30, %		26.6	30.0	31.5	39.2	45.1
PR (95% CI)		0.86 (0.72-1.03)	0.96 (0.84-1.10)	1 (ref)	1.23 (1.10-1.39)	1.42 (1.20-1.68)
BMI 30-35, %		27.8	31.4	31.5	28.5	26.7
PR (95% CI)		0.87 (0.72-1.03)	1.01 (0.88-1.15)	1 (ref)	0.91 (0.80-1.03)	0.88 (0.70-1.10)
BMI 35-40, %		19.4	17.6	15.7	12.7	6.4
PR (95% CI)		1.22 (0.96-1.56)	1.12 (0.92-1.37)	1 (ref)	0.83 (0.67-1.02)	0.44 (0.27-0.71)
BMI >40, %		19.4	11.1	8.0	3.9	1.5
PR (95% CI)		2.41 (1.83-3.18)	1.37 (1.04-1.80)	1 (ref)	0.51 (0.36-0.74)	0.21 (0.08-0.57)
Waist-to-hip ratio, m (IQR)	4	0.97 (0.92-1.03)	1.00 (0.98-1.03)	1 (ref)	0.98 (0.96-1.00)	0.92 (0.88-0.96)
Central obesity[I], %		87.8	92.8	92.5	90.6	84.9
PR (95% CI)		0.95 (0.92-0.98)	1.00 (0.98-1.03)	1 (ref)	0.98 (0.96-1.00)	0.92 (0.87-0.96)
Weight gain since age 20 years, kg, m (IQR)	1050	17 (7-30)	22 (11-33)	22 (12-33)	19 (11-29)	14 (7-23)
Weight gain >20 kg since age 20, %		44.6	55.4	55.8	48.4	36.5
PR (95% CI)		0.80 (0.71-0.90)	0.99 (0.92-1.07)	1 (ref)	0.87 (0.80-0.94)	0.66 (0.56-0.77)
Blood pressure, mmHg, m (IQR)						
Hypertension[II], %	30	31.7	35.7	34.4	35.5	33.3
PR (95% CI)		0.92 (0.80-1.07)	1.04 (0.93-1.16)	1 (ref)	1.03 (0.94-1.14)	0.97 (0.83-1.14)
Total cholesterol, mmol/L, m (IQR)	2096	4.7 (3.9-5.3)	4.4 (3.8-5.2)	4.3 (3.7-5.1)	4.3 (3.7-5.0)	4.2 (3.6-4.9)
Triglycerides, mmol/L, m (IQR)	357	2.1 (1.3-3.2)	1.8 (1.3-2.7)	1.6 (1.2-2.3)	1.5 (1.1-2.1)	1.4 (1.1-1.9)
HDL cholesterol, mmol/L, m (IQR)	2085	1.0 (0.9-1.2)	1.1 (1.0-1.3)	1.2 (1.0-1.5)	1.3 (1.1-1.6)	1.3 (1.1-1.7)
LDL cholesterol, mmol/L, m (IQR)	184	2.4 (1.9-3.0)	2.4 (1.8-3.0)	2.2 (1.7-2.8)	2.1 (1.6-2.7)	2.0 (1.6-2.7)
LDL cholesterol > 2.5 mmol/L, %		49.6	45.6	37.9	33.4	30.9
PR (95% CI)		1.31 (1.17-1.46)	1.21 (1.10-1.32)	1 (ref)	0.88 (0.80-0.97)	0.82 (0.69-0.96)
Dyslipidemia[III], %	895	90.0	86.0	78.9	72.3	68.0
PR (95% CI)		1.14 (1.10-1.19)	1.09 (1.05-1.13)	1	0.92 (0.88-0.96)	0.86 (0.79-0.93)
CRP, mg/L[IV], m (IQR)	4267	3.2 (1.2-6.4)	2.5 (1.1-5.8)	1.9 (0.8-4.4)	1.8 (0.9-3.7)	1.6 (0.8-3.4)
CRP >3.0 mg/L, %		53.0	44.4	37.6	29.4	25.5
PR (95% CI)		1.41 (1.12-1.78)	1.18 (0.95-1.47)	1 (ref)	0.78 (0.61-1.01)	0.68 (0.42-1.11)
Hospital-diagnosed retinopathy, %	0	7.2	3.5	4.5	3.9	3.8
PR (95% CI)		1.58 (1.08-2.31)	0.77 (0.52-1.12)	1 (ref)	0.86 (0.61-1.20)	0.85 (0.49-1.45)
Albumin-creatinine ratio, mg/g, m (IQR)	610	9.0 (5.0-22.0)	8.0 (3.0-22.1)	4.0 (9.0-21.0)	4.0 (9.0-22.0)	12 (5.8-36.0)
≥30, %		21.8	19.4	19.1	20.3	27.5
PR (95% CI)		1.14 (0.93-1.40)	1.02 (0.86-1.20)	1 (ref)	1.06 (0.91-1.23)	1.44 (1.18-1.76)

Estimates are shown as percentages (%), medians (m) with interquartile ranges (IQR), or prevalence ratios (PR) with 95% confidence Intervals (95% CI).

*Adjusted for time since commencement of glucose-lowering pharmacological treatment to enrolment in the DD2 cohort.

[I]Waist-to-hip ratio > 0.85/>0.90 for men/women.

[II]Systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg.

[III]LDL cholesterol >2.60 mmol/L, or HDL cholesterol <1.02 mmol/L, or triglyceride >1.7 mmol/L.

[IV]Only available for a subset of 840 cohort members.

higher likelihood of receiving any GLD, and a 3.6-fold higher likelihood of receiving several GLDs, within the first year.[27] Two large cohort studies[28,29] in Danish background populations identified an age-gradient with higher prevalence of hypertension in older individuals. When comparing these findings with the prevalence found in our study (~30% with hypertension in all age groups), the prevalence of hypertension among the early-onset individuals was higher than in a similar-aged background population, whereas the prevalence among the late-onset individuals was lower than in a similar-aged background population.

Health behaviour is likely to contribute to the observed adverse clinical profile of the early-onset group. A large cross-sectional study

TABLE 3 Behavioural risk factors among 5115 persons with newly diagnosed type 2 diabetes in 5 groups defined by age at diagnosis

		Age at Diagnosis				
Behavioural Risk Factors	Missing n	≤45 years n = 516	46-55 years n = 1091	56-65 years *n* = 1651	66-75 years *n* = 1466	>75 years *n* = 391
Physical activity[I], days/week, m (IQR)	0	3 (2-5)	3 (1-6)	4 (2-7)	4 (2-7)	4 (1-7)
0-3, %		56.2	54.6	48.1	46.3	49.6
PR (95% CI)		1.17 (1.07-1.28)	1.14 (1.06-1.22)	1 (ref)	0.96 (0.89-1.04)	1.03 (0.92-1.15)
4-5, %		21.5	20.0	19.5	17.5	15.6
PR (95% CI)		1.10 (0.91-1.34)	1.03 (0.88-1.20)	1 (ref)	0.90 (0.77-1.04)	0.80 (0.62-1.03)
6-7, %		22.3	25.4	32.4	36.3	34.8
PR (95% CI)		0.69 (0.58-0.82)	0.78 (0.69-0.89)	1 (ref)	1.12 (1.02-1.23)	1.07 (0.92-1.25)
Daily smoking, %	271	23.8	23.7	20.3	12.9	7.9
PR (95% CI)		1.18 (0.98-1.42)	1.17 (1.01-1.36)	1 (ref)	0.64 (0.54-0.75)	0.39 (0.27-0.56)
High-risk alcohol intake[II], %	0	3.7	6.1	7.3	8.7	4.6
PR (95% CI)		0.50 (0.31-0.81)	0.84 (0.63-1.12)	1 (ref)	1.19 (0.94-1.51)	0.63 (0.39-1.02)

Estimates are shown as percentages (%), medians (m) with interquartile ranges (IQR), or prevalence ratios (PR) with 95% confidence Intervals (95% CI).

[I]Days per week where cohort members report at least 30 minutes of moderate to vigorous physical activity.

[II]Alcohol intake >14/21 drinks per week for women/men.

TABLE 4 Therapy among 5115 persons with newly diagnosed type 2 diabetes in 5 groups defined by age at diagnosis

		Age at Diagnosis				
Therapy	Missing n	≤45 years n = 516	46-55 years n = 1091	56-65 years n = 1651	66-75 years n = 1466	>75 years n = 391
Glucose-Lowering Drugs	0					
No glucose-lowering drugs, %		8.1	12.3	14.6	17.5	21.5
PR (95% CI)		0.56 (0.41-0.76)	0.84 (0.69-1.02)	1 (ref)	1.20 (1.02-1.41)	1.47 (1.18-1.84)
Non-insulin drugs, %		80.0	78.2	78.4	77.7	75.2
PR (95% CI)		1.02 (0.97-1.07)	1.00 (0.96-1.04)	1 (ref)	0.99 (0.96-1.03)	0.96 (0.90-1.02)
Insulin only, %		1.4	1.8	1.2	0.6	1.0
PR (95% CI)		1.18 (0.50-2.79)	1.59 (0.85-2.97)	1 (ref)	0.53 (0.24-1.18)	0.89 (0.30-2.60)
Insulin and non-insulin drugs, %		10.5	7.7	5.9	4.2	2.3
PR (95% CI)		1.78 (1.30-2.45)	1.31 (0.99-1.74)	1 (ref)	0.72 (0.53-0.98)	0.39 (0.20-0.77)
Duration of glucose-lowering treatment before DD2 enrolment[I], month, m(IQR)		12.8 (3.0-27.5)	14.3 (2.8-28.8)	17.1 (3.9-32.1)	18.7 (5.3-33.8)	21.2 (8.7-34.5)
Antihypertensive drugs, %	0	39.5	63.4	76.3	83.4	90.0
PR (95% CI)		0.52 (0.46-0.58)	0.83 (0.79-0.88)	1 (ref)	1.09 (1.05-1.13)	1.18 (1.13-1.23)
Lipid-lowering drugs, %	0	53.9	67.5	76.6	78.4	74.7
PR (95% CI)		0.70 (0.65-0.77)	0.88 (0.84-0.93)	1 (ref)	1.02 (0.99-1.06)	0.98 (0.92-1.04)
Anticoagulation drugs, %	0	7.4	21.4	32.3	40.2	44.8
PR (95% CI)		0.23 (0.17-0.31)	0.66 (0.58-0.76)	1 (ref)	1.25 (1.33-1.37)	1.39 (1.22-1.58)
Eye screening completed[II], %	0	56.2	54.5	56.2	52.8	45.0
PR (95% CI)		1.00 (0.92-1.09)	0.97 (0.90-1.04)	1 (ref)	0.94 (0.88-1.00)	0.80 (0.71-0.90)
Foot screening completed[II], %	0	82.0	84.0	86.3	85.9	87.0
PR (95% CI)		0.95 (0.91-0.99)	0.97 (0.94-1.01)	1 (ref)	1.00 (0.97-1.02)	1.01 (0.97-1.05)

Estimates are shown as percentage (%), median (m) with interquartile range (IQR), or prevalence ratio (PR) with 95% confidence Intervals (95% CI).

[I]Months since commencement of glucose-lowering pharmacological treatment to DD2 enrolment.

[II]Examination of foot or eye registered in the year prior to or after enrolment.

found a lower physical activity level among persons with early-onset type 2 DM than among those with later-onset type 2 DM.[16] The smoking prevalence of 24% in the early-onset group in our study was not only higher than in the later-onset groups but is also higher than the Danish national average of 18% in a similar age group (35-44 years)[30]. Similarly, in the United States, smoking prevalence

among less than 40-year-old individuals was reported at 25% and 20% among persons with and without type 2 DM.[30]

As in other studies,[16,31] we found that antihypertensive, lipid-lowering, and anticoagulation drugs were used less often by persons with early-onset type 2 DM, in spite of their worse risk factor profile. This indicates a problem of under-treatment. The identified presence of GAD antibody positive individuals among people with clinically diagnosed type 2 DM suggests that there may be pitfalls in diabetes diagnosing in routine clinical practice.

Our findings are disquieting considering the consistent findings of a high risk of later diabetes complications in persons with early-onset type 2 DM.[7,9,11,31,32] One study found that after 20 years of diabetes duration, 37% of persons diagnosed before the age of 40 years had developed cardiovascular disease, and the early-onset individuals appeared to develop microvascular complications 13 to 20 years earlier than later-onset individuals.[11] Gregg et al.[12] showed that the overall improvements in diabetes outcomes observed during the last 20 years are primarily due to a reduction in complications among older persons with type 2 DM. Therefore, the increased incidence of type 2 DM in high-risk young persons could cause a future rise in diabetes complications.[12]

4.1 | Strength and limitations

The main strength of our study was the comprehensiveness of uniformly collected data in a large incident cohort of persons clinically diagnosed with type 2 DM. The linkage of clinical and self-reported information with data from high-quality national health registers allowed for a full description of risk factors. For some risk factors, such as anthropometric measures and laboratory values, there were missing data, and missing data were somewhat more common in the elderly than younger age groups in our cohort (data not shown). A slightly lower completeness of risk factor values by older age would not necessarily bias our findings, unless completeness was related both to age and to the actual value of the data, which we find less likely. Availability of laboratory values was related to calendar period of data in the biobank, not to age group.

The cross-sectional study design is an inborn limitation, as it implies uncertainty regarding how the risk factors preceded each other, and impedes knowledge about the development over time in risk profiles. Moreover, there is an over-representation of persons with type 2 DM receiving hospital-based versus primary care in the DD2 cohort. Consequently, since both young age and a high risk-factor level in type 2 DM may lead to referral from GP to outpatient hospital care, relatively more high-risk individuals may have been recruited into the cohort among early- than among later-onset type 2 DM individuals, leading to a Berkson-like bias and a possible overestimation of risk factor prevalence in the early-onset group.

5 | CONCLUSION

In conclusion, our study identified an increasing prevalence of clinical and behavioural risk factors the younger the onset age of type 2 DM, emphasizing that early-onset type 2 DM is not a benign condition. Our results underline the need for clinical awareness and multifactorial interventions among early-onset type 2 diabetes patients and a need for prospective studies exploring the association between early risk factors and development of diabetes-related complications.

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DISCLOSURE OF INTERESTS

None declared

AUTHOR CONTRIBUTIONS

HBN, HTS, JR, TKH, JS, SF, TL, JSN, and RWT participated in designing the DD2 cohort. JSN, RWT, HTM, SKN, and AB conceived the study. SKN performed the statistical analysis. AB initially drafted the article, with help by HTM, RWT, and JSN. All authors contributed substantially, revised the manuscript for intellectual content, and approved the final version to be submitted.

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