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High prevalence of retinopathy in young-onset type 2 diabetes and possible sex differences: insights from Norwegian general practice

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ABSTRACT

Introduction People with young-onset type 2 diabetes (YOD), defined as diabetes diagnosis before age 40, have a high lifetime risk of vascular complications. We aimed to estimate the prevalence of YOD among adults with type 2 diabetes (T2D) in Norwegian general practice and explore associations between age at diabetes diagnosis and retinopathy overall and in men and women.

Research design and methods We collected cross-sectional data from general practice electronic medical records of 10 241 adults with T2D in 2014, and repeated measurements of hemoglobin A_{1c} (HbA_{1c}) from 2012 to 2014. Using multivariate logistic regression, we assessed associations between YOD and later-onset T2D, sex and retinopathy.

Results Of all individuals with T2D, 10% were diagnosed before 40 years of age in both sexes. Compared with later-onset T2D, HbA_{1c} increased faster in YOD, and at the time of diagnosis HbA_{1c} was higher in men, particularly in YOD. Retinopathy was found in 25% with YOD, twice as frequently as in later onset. After adjustments for confounders (age, country of origin, education, body mass index), OR of retinopathy was increased in both men with YOD (OR 2.6 (95% CI 2.0 to 3.5)) and women with YOD (OR 2.2 (1.5 to 3.0)). After further adjustments for potential mediators (diabetes duration and HbA_{1c}), the higher OR persisted in men with YOD (OR 1.8 (1.3 to 2.4)) but was attenuated and no longer significant for women with YOD.

Conclusions Retinopathy prevalence was more than twice as high in YOD as in later-onset T2D. The increased likelihood of retinopathy in YOD was partly mediated by higher HbA_{1c} and longer T2D duration, but after accounting for these factors it remained higher in men with YOD.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Type 2 diabetes (T2D) with young onset (YOD) is increasingly common and associated with adverse diabetes outcomes.

WHAT THIS STUDY ADDS

⇒ Among both men and women, we found that 10% with T2D in Norwegian general practice were diagnosed before age 40 (YOD) and these individuals had a more than doubled likelihood of retinopathy compared with later-onset T2D.

⇒ Higher likelihood of retinopathy in YOD was partly explained by higher hemoglobin A_{1c} (HbA_{1c}) and longer diabetes duration, but remained increased in men with YOD after accounting for these mediating factors.

⇒ Higher HbA_{1c} at diagnosis in men versus women with YOD, potentially indicatory of delayed T2D diagnosis in men with YOD, may account for their remaining excess likelihood of retinopathy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings may highlight a need for more focused efforts to prevent retinopathy in people with YOD, and a possible need for earlier diagnosis of T2D, especially among young men.

INTRODUCTION

Type 2 diabetes (T2D) has increased globally, especially in younger adults.[1] Still, studies reporting prevalence of young-onset T2D (YOD), defined as diabetes diagnosis before age 40, are scarce.[2] YOD is associated with higher complication rates and reduced life expectancy.[3 4] Recent reductions in adverse outcomes in T2D have been less evident in YOD.[5 6]

Individuals with YOD have higher body mass index (BMI) and hemoglobin A_{1c} (HbA_{1c}) than in later-onset T2D and retinopathy is the diabetes complication with highest excess risk.[7–9] In T2D, incidence of retinopathy and symptomatic eye disease has been reduced due to less smoking, better glycemic and blood pressure control, and earlier detection and treatment.[10] However, it is less known to what extent individuals with YOD have benefited. In YOD, longer diabetes duration and poorer glycemic control seem to be the most important factors explaining higher prevalence of retinopathy, but it is unresolved

whether YOD is an inherently more aggressive disease phenotype.[9 11]

In men, the absolute risk of acquiring T2D and YOD and of developing diabetes complications is higher compared with women.[1 12 13] Men also develop T2D at lower BMI.[14] Sex differences in macrovascular complications are widely studied, while population-based or primary care studies comparing microvascular complications by sex are scarce. Therefore, we aimed to identify the prevalence of diabetes onset before age 40 among adults with T2D in Norwegian general practice and investigate associations between YOD and retinopathy overall and stratified by sex.

Research design and methods

Design, data collection and participants

Data source was the ROSA 4 study, described in detail elsewhere.[15 16] In short, ROSA 4 is a cross-sectional dataset on all individuals with a diabetes mellitus diagnosis identified in the electronic medical records (EMRs) of 282 Norwegian general practitioner (GPs). Data were collected in 2015 from three of four health regions. We invited smaller and larger practices from both urban and rural areas of low and high socioeconomic status and mixed ethnic backgrounds. For the included GPs, age, sex distribution and number of patients on their lists were comparable with the Norwegian average.[15] Data include patients' sex, year of birth and diabetes diagnosis, diabetes type, relevant clinical examinations and laboratory results, diabetic complications, prescribed diabetes medications, referrals for diabetes to and summaries from secondary healthcare.

Data on adults (≥18 years), with a diabetes diagnosis recorded in each GP's EMR between 2012 and 2014, were extracted using a customized software program (Medrave). Research nurses manually validated all diagnoses and year of diagnosis according to the study protocol. The dataset comprised 11 428 diabetes cases; 10 248 with T2D, 1180 with T1D and 49 with other or unknown type.[15] For individuals with age of onset <50 years, three clinicians used medication history and clinical data to quality check diabetes type. Some cases (<10) were reclassified, resulting in 10 241 cases with T2D. Education and country background variables from Statistics Norway were linked to ROSA 4.[17]

Variables

The exposure variable, age at diabetes diagnosis, was stratified into three groups: diagnosis (1) before age 40 years (YOD), (2) age 40–49 years and (3) 50 years or older.

The primary outcome was retinopathy diagnosed by an ophthalmologist, registered in the GP's EMR as a diagnosis code, free text or in notes from secondary care. Treatment of retinopathy with injections, laser or other methods was recorded, including year of first treatment. Impaired vision was recorded as visual acuity lower than 0.33.

The last recorded clinical measurements before January 1, 2015 were included. For hemoglobin A_{1c} (HbA_{1c} %, converted to mmol/mol), 95% of individuals had repeated measurements from 2012 to 2014, with an average of seven recordings per person. Of these, 1836 (19%) were diagnosed with T2D in this time period and thus had a recorded HbA_{1c} at diagnosis. Reduced foot sensibility/neuropathy, coronary heart disease and stroke were recorded from GPs' EMR including secondary care notes. Chronic kidney disease was defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2. Glucose-lowering treatment was categorized as either: (1) no antidiabetic medication or "diet only," (2) "insulin," alone or in combination with other agents or (3) "other glucose-lowering agents" only. Current smokers were defined as smoking recorded during the last 5 years. Highest education was categorized as compulsory education (primary and lower secondary), upper secondary or higher education. Country of origin was divided into three groups, Europe and North America, South Asia and other.

Statistical analysis

Descriptive statistics are presented with means, proportions and 95% CIs as appropriate. Individuals with and without a recorded year of diagnosis and retinopathy status were compared descriptively. Statistical analyses were undertaken in StataSE16 (StataCorp).

Associations between age at diabetes diagnosis, either age or diabetes duration and diabetes complications were estimated using logistic regression. Further, average adjusted predictions (AAPs) of complications in each age-at-onset group were calculated using the margins command. AAPs give the expected average complication prevalence over the observed distribution of current age or diabetes duration if all individuals were diagnosed before age 40, at age 40–49 or at age 50 years.

A directed acyclic graph was drawn in Dagitty V.3.0 prior to analysis to identify possible clinically relevant relationships between exposure (YOD), primary outcome (retinopathy) and potential confounding and mediating variables (online supplemental figure 1).

HbA_{1c} progression was analyzed using longitudinal data. Average HbA_{1c} was estimated by age at diagnosis and diabetes duration, using the first observed measurement in each year. Average HbA_{1c} progression in the first year was analyzed by estimating local linear regressions by sex and age at diagnosis, using the lpoly command. Associations between age at diagnosis, sex and HbA_{1c} up to 10 years diabetes after diagnosis were analyzed by linear regression.

To reduce potential bias from missing values for retinopathy, multilevel multiple imputation was undertaken in R V.3.5.2 under the assumption of missing at random. The R package miceadds was used to generate 25 imputed datasets, exported to Stata for analysis.

Multivariate logistic regression analyses were undertaken in imputed data and in complete cases, to assess associations between YOD and retinopathy, stratified

by sex. In Model 1, all identified potential confounders (age, education, country of origin, BMI) were adjusted for. In Model 2, potential mediators (HbA_{1c}, diabetes duration, systolic blood pressure, low-density lipoprotein (LDL) cholesterol) were added. All covariates were tested for interactions by cross-product terms, but no significant interactions were found. Potential mediators were included in the final models if the absolute difference in OR for retinopathy was more than 0.1.

Regression analyses were repeated for complete cases and for missing values for retinopathy assigned to "no retinopathy." Results are presented as adjusted OR (aOR) with 95% CIs.

Predicted retinopathy prevalences based on the imputed logistic regression analyses were plotted using mimargins and marginsplot.

RESULTS

Sample characteristics

Characteristics of the 10241 individuals with T2D are presented in table 1, and separately for women and men in online supplemental table 1). Mean age was 65 (±13) years, 55% were men and 15% had non-Western background. Year of diabetes diagnosis was recorded in 9605 (94%). Average age at diagnosis was 56 (±13) years and diabetes duration 8.6 (±7.0) years. Ten percent (both among men and women) were younger than 40 years at diabetes diagnosis (YOD). Only six individuals were diagnosed before 18 years of age. Mean age in YOD was 33 (±5.1) years at diabetes diagnosis and 45 (±10) years in 2014. Mean diabetes duration was longer and BMI higher in YOD than in later-onset T2D. Glucose-lowering treatment was prescribed to a higher proportion and more intensively in YOD than in later-onset T2D. Insulin was given almost three times as often in YOD as in the oldest onset group in both men and women. In YOD, prescribed glucose-lowering treatment was more intensive for a given level of HbA_{1c} (data not shown).

Prevalence of diabetes complications

Unadjusted prevalence of retinopathy was 13% overall and 25% in YOD, while all other complications were less common in YOD than in later-onset T2D (table 2). Regardless of age at diabetes onset, all complications were more prevalent among men than women (online supplemental tables 2 and 3). When adjusted for current age, complications were predicted to be more prevalent in YOD (table 2). Fundus examination was only recorded in 60%, hence retinopathy status was missing in 40% (tables 1 and 2). Those with unknown retinopathy status had less intensive glucose-lowering treatment and shorter diabetes duration on average, and more had non-Western backgrounds (online supplemental table 4). Other characteristics, including distribution of age at diagnosis, were similar in those with known and unknown retinopathy status.

Of all individuals in the dataset, 1.7% had undergone treatment for retinopathy (2.4% of those with known retinopathy status), 4.6% in YOD, 2.8% in age 40–49 at diabetes diagnosis, and 1.1% in onset at age 50 and older. Of men with YOD, 5.7% had undergone retinopathy treatment, compared with 3.2% of women with YOD (p=0.07). For men with YOD, a trend was observed of shorter time from diabetes diagnosis to first retinopathy treatment and higher frequency of visual impairment compared with later-onset diabetes and women with YOD . However, these differences were not statistically significant (data not shown).

Associations between age at diabetes onset, sex and retinopathy

Using the imputed dataset and after adjustment for confounders, retinopathy prevalence increased more steeply after T2D diagnosis in YOD than in later-onset T2D and more among men than women (figure 1). In logistic regression analyses, aOR for retinopathy in YOD was found to be 2.4 (2.0 to 3.0) compared with those with a diabetes diagnosis at 50 years or older. Men had an aOR for retinopathy of 1.6 (1.4 to 1.8) compared with women, but there was no interaction between sex and age at diabetes diagnosis on OR for retinopathy (data not shown in table). Focusing on men and women with YOD, both sexes had significantly increased OR for retinopathy compared with later onset after adjustments for confounders (table 3, Model 1, aOR men with YOD 2.6 (2.0 to 3.5), aOR women with YOD 2.2 (1.5 to 3.0)). With further adjustments for potential mediators (diabetes duration and HbA_{1c}, Model 4), men with YOD still had higher OR for retinopathy, while women with YOD no longer had a significantly increased OR. Both mediators reduced aOR for retinopathy, with diabetes duration giving the greatest reduction (Model 3). LDL cholesterol and blood pressure were omitted from the final regression as they altered OR for retinopathy in YOD less than 0.1 (data not shown).

Analyses of complete cases (n=3154) and of missing values for retinopathy assigned to "no retinopathy" provided similar findings (online supplemental tables 5 and 6). Analyzing age at diabetes diagnosis as a continuous variable and adjusting for current age, OR for retinopathy was reduced by 10% for each year higher age at diabetes diagnosis (OR 0.90 (0.89 to 0.90)).

The possible impact of HbA_{1c} at diagnosis

Using the longitudinal dataset for both sexes combined, we observed at least one HbA_{1c} measurement in the year of diabetes diagnosis for 1836 individuals. Among these, the mean first HbA_{1c} was significantly higher for those with diabetes onset before 50 years of age than those with later onset (figure 2A). One year after diagnosis, HbA_{1c} had declined in all groups and differences by age at onset were no longer statistically significant. Thereafter, HbA_{1c} showed steeper increase over the first 5 years in YOD compared with later-onset T2D. Zooming

Table 1 Characteristics of patients with type 2 diabetes stratified by age at diagnosis. Both sexes combined

			Year of diagnosis				
			Unknown	Known	Age diabetes diagnosis (years)		
	Valid data n (%)	Total sample	All ages	All ages	<40	40–49	≥50
Patient characteristics							
Total study participants, n (%)	10241	10241	636	9605	980 (10)	1998 (21)	6627 (69)
Sex, men, n (%)	10241 (100)	5625 (55)	324 (51)	5301 (55)	545 (56)	1219 (61)	3537 (53)
Age at diagnosis, mean years (SD)	9605 (94)	56 (13)	N/A	56 (13)	33 (5.1)	45 (2.8)	63 (8.7)
Age in 2014, mean years (SD)	10241 (100)	65 (13)	67 (14)	65 (13)	45 (10)	55 (8.3)	70 (10)
Diabetes duration, mean years (SD)	9605 (94)	8.6 (7.0)	N/A	8.6 (7.0)	11.4 (9.0)	10.0 (8.0)	7.8 (6.1)
Country of origin, n (%)							
Europe or North America	10241 (100)	8642 (85)	495 (78)	8147 (85)	599 (61)	1503 (75)	6045 (91)
South-Asia	10241 (100)	817 (8.0)	67 (11)	750 (7.8)	216 (22)	252 (13)	282 (4.3)
Other	10241 (100)	782 (7.6)	74 (12)	708 (7.4)	165 (17)	243 (12)	300 (4.5)
Highest education level, n (%)							
Compulsory (primary and lower secondary)	9879 (97)	3509 (36)	222 (38)	3287 (35)	373 (41)	681 (36)	2233 (35)
Upper secondary	9879 (97)	4518 (46)	263 (45)	4255 (46)	357 (39)	820 (43)	3078 (48)
Higher	9879 (97)	1852 (19)	101 (17)	1751 (19)	186 (20)	397 (21)	1168 (18)
Clinical characteristics, mean (SD)							
BMI	4651 (45)	30.2 (6.0)	30.6 (7.3)	30.2 (5.9)	32.1 (6.7)	31.3 (6.2)	29.4 (5.5)
Current smoker, n (%)	8070 (79)	1825 (23)	88 (28)	1737 (22)	195 (26)	458 (28)	1084 (20)
HbA_{1c} (mmol/mol)	9929 (97)	53 (13)	53 (13)	53 (13)	59 (17)	56 (15)	52 (12)
HbA_{1c} (%)	9929 (97)	7.0 (1.2)	7.0 (1.2)	7.0 (1.2)	7.6 (1.6)	7.3 (1.4)	6.9 (1.1)
Systolic BP (mmHg)	8954 (87)	135 (17)	137 (17)	135 (17)	130 (16)	133 (16)	137 (17)
LDL cholesterol (mmol/L)	8580 (84)	2.8 (0.9)	2.8 (1.0)	2.8 (0.9)	2.8 (0.9)	2.8 (0.9)	2.7 (0.9)
Cholesterol ratio, total/HDL	8720 (85)	4.0 (1.2)	4.0 (1.2)	4.0 (1.2)	4.5 (1.4)	4.3 (1.3)	3.9 (1.2)
eGFR (mL/min/1. 73 m^2)	9699 (95)	81 (21)	77 (23)	82 (21)	101 (19)	92 (18)	76 (20)
Medical treatment, n (%)							
Diet only	10238 (100)	2855 (28)	163 (26)	2692 (28)	139 (14)	384 (19)	2169 (33)
Other glucose-lowering agents	10241 (100)	6573 (64)	406 (64)	6167 (64)	734 (75)	1456 (73)	3977 (60)
Insulin	10223 (100)	1786 (18)	121 (19)	1665 (17)	340 (35)	467 (23)	858 (13)
Eye examination, n (%)							
Fundus exam performed	6142	6142 (60)	222 (35)	5920 (62)	599 (61)	1243 (62)	4078 (62)

BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 2 Complications by age at diabetes diagnosis. Unadjusted prevalences and average predictions adjusted for mean age or diabetes duration

	Valid data n (%)	Total sample	Year of diagnosis		Age at diabetes diagnosis (years)		
			Unknown	Known			
			All ages	All ages	<40	40–49	≥50
Complications, n (%) unadjusted							
Retinopathy	6086 (60)	797 (13)	30 (15)	767 (13)	152 (25)	226 (18)	389 (9.7)
Chronic kidney disease*	9699 (95)	1596 (17)	134 (24)	1462 (16)	35 (3.9)	107 (5.7)	1320 (21)
Reduced foot sensibility/neuropathy	2733 (38)	302 (11)	11 (16)	291 (11)	23 (8.5)	60 (9.7)	208 (12)
CHD	10217 (100)	2258 (22)	146 (23)	2112 (22)	93 (9.5)	316 (16)	1703 (26)
Stroke	10226 (100)	756 (7.4)	50 (7.9)	706 (7.4)	24 (2.5)	85 (4.3)	597 (9.0)
AAP - complications, % (95% CI) adjusted for current age							
Retinopathy	5880				46 (41 to 52)	26 (23 to 29)	8.0 (7.2 to 8.8)
Chronic kidney disease*	9135				28 (23 to 34)	20 (17 to 22.2)	15 (15 to 17)
Reduced foot sensibility/neuropathy	2663				16 (9.5 to 22)	13 (9.9 to 17)	10 (8.7 to 11)
CHD	9581				24 (20 to 28)	25 (23 to 28)	21 (20 to 22)
Stroke	9590				8.2 (5.0 to 11.4)	8 (6.5 to 10)	7.2 (6.6 to 7.8)
AAP - complications, % (95% CI) adjusted for diabetes duration							
Retinopathy	5880				19 (16 to 22)	15 (13 to 17)	11 (10 to 12)
Chronic kidney disease*	9135				2.4 (1.6 to 3.3)	4.7 (3.8 to 5.5)	22 (22 to 24)
Reduced foot sensibility/neuropathy	2663				7.1 (4.2 to 10)	9.0 (6.8 to 11)	12 (11 to 14)
CHD	9581				7.9 (6.4 to 9.5)	15 (13 to 16)	27 (26 to 28)
Stroke	9590				2.1 (1.2 to 2.9)	3.9 (3.1 to 4.7)	9.5 (8.8 to 10)

Average adjusted predictions (AAPs) calculated by logistic regression followed by the margins command in Stata.
*eGFR <60 mL/min/1.73 m^2
CHD, coronary heart disease.

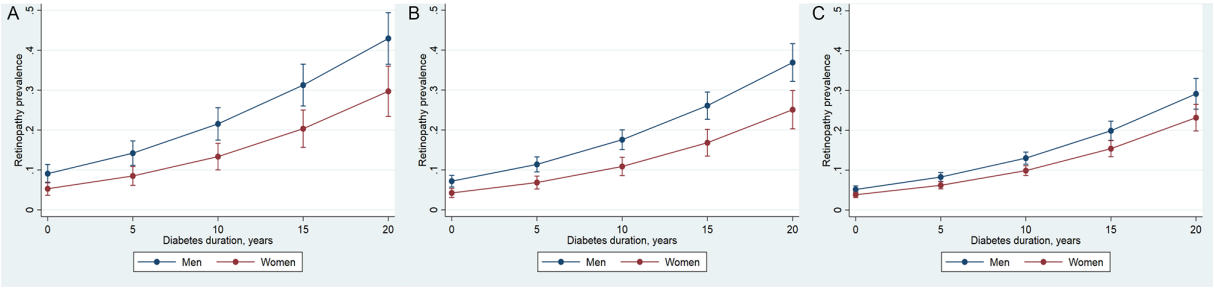

Figure 1 Predicted prevalence of retinopathy with increasing diabetes duration by sex and age at diagnosis: (A) <40 years at diabetes diagnosis (young onset type 2 diabetes); (B) 40–49 years at diagnosis; (C) 50 years and older. Based on logistic regression with diabetes duration adjusting for age, country background, education level and body mass index. Vertical bars represent 95% CIs.

in on development of HbA_{1c} during the first year from diagnosis in men and women separately, men with YOD started with a mean HbA_{1c} of 8.8% (8.4 to 9.1%), significantly and substantially higher than women with YOD, at 7.4% (7.0 to 7.9%) (figure 2B). In later-onset T2D, average HbA_{1c} at diagnosis was also significantly higher in men, but with a smaller absolute difference of 7.9% (7.8 to 8.0%) versus 7.5% (7.4 to 7.7%) (figure 2C). For all ages and both sexes, HbA_{1c} fell within the first 100 days and then stabilized at around 7% in YOD and slightly lower levels in later onset for the remainder of the first year. Linear regression of HbA_{1c} by diabetes duration the first 10 years showed significant differences between men and women in HbA1c over time (online supplemental table 7). This difference was substantially greater in YOD than in later-onset T2D, with the greatest sex differences seen at diagnosis. However, there was no interaction between sex and diabetes duration, the development of HbA_{1c} showing the similar trends in both sexes. This finding is supported by online supplemental figure 2, which displays the development in yearly mean HbA_{1c} for all age-at-diagnosis strata and for each sex over 10 years. We see the same initial decline in HbA_{1c} the first year after diagnosis, and subsequent steeper and greater increase of HbA_{1c} in YOD with longer diabetes duration. Trends are different in YOD and later-onset T2D, but similar for men and women.

DISCUSSION

To our knowledge, this is one of very few population-based studies of retinopathy in YOD, and the first to investigate how sex impacts the association between YOD and retinopathy. For both men and women, 10% of T2D had been diagnosed before age 40. Overall, 13% had a retinopathy diagnosis. After adjustments for confounders, OR for retinopathy was more than doubled in YOD compared with diabetes onset after 50 years of age, and men had 60% higher OR for retinopathy than women. In YOD, both sexes had significantly increased likelihood of retinopathy compared with later onset after adjustments for confounders. After additional adjustment for the key mediators HbA_{1c} and diabetes duration, men with YOD still had an increased OR for retinopathy, while it was no longer significant for women with YOD. The remaining excess likelihood of retinopathy in men with YOD may

Table 3 ORs for having retinopathy by age at T2D diagnosis and sex—imputed data

		Unadjusted	Model 1	Model 2	Model 3	Model 4
YOD						
	Men	**3.0 (2.4 to 3.8)**	**2.6 (2.0 to 3.5)**	**2.2 (1.7 to 3.0)**	**1.9 (1.4 to 2.6)**	**1.8 (1.3 to 2.4)**
	Women	**2.5 (1.8 to 3.3)**	**2.2 (1.5 to 3.0)**	**1.8 (1.2 to 2.5)**	**1.5 (1.0 to 2.1)**	1.3 (0.91 to 1.9)
Age 40–49 at diagnosis						
	Men	**2.0 (1.6 to 2.4)**	**1.8 (1.5 to 2.3)**	**1.6 (1.3 to 2.0)**	**1.5 (1.2 to 1.8)**	**1.4 (1.1 to 1.7)**
	Women	**1.6 (1.2 to 2.1)**	**1.5 (1.2 to 2.0)**	**1.3 (1.0 to 1.7)**	1.1 (0.85 to 1.5)	1.1 (0.79 to 1.4)
N		10238	10238	10238	10238	10238
Number of imputed datasets			25	25	25	25

Exponentiated coefficients; 95% CIs in brackets.
Reference: T2D diagnosis age 50 or older.
Significant estimates in bold.
Model 1: adjusted for confounders: age, non-Western background, compulsory education and body mass index. Model 2: Model 1 and additionally adjusted for HbA_{1c}. Model 3: Model 1 and additionally adjusted for diabetes duration. Model 4: Model 1 and additionally adjusted for HbA_{1c} and diabetes duration.
HbA_{1c}, hemoglobin A_{1c}; T2D, type 2 diabetes; YOD, young-onset T2D.

Figure 2 HbA_{1c} progression with diabetes duration by sex and age at diagnosis. (A) First HbA1c measurements for each person and year from 2012 to 2014 by diabetes duration. Both sexes combined. Three age-at-diagnosis groups: <40 years (YOD, young-onset T2D), 40–49 years, 50 years and older. Vertical bars represent 95% CIs. The points are displaced along the x-axis to reduce overlap. (B) Average HbA_{1c} by sex and days since first HbA_{1c} measurement, age at diagnosis <40 years (YOD). Average HbA_{1c} estimated by local linear regressions (bandwidth 30 days, Epanechnikov kernel). Confidence bands show 95% CIs. (C) Average HbA_{1c} by sex and days since first HbA_{1c} measurement, age at diagnosis 40 years or older. HbA_{1c}, hemoglobin A_{1c}; T2D, type 2 diabetes.

be related to our finding of higher HbA_{1c} at the point of diabetes diagnosis in men versus women with YOD. This finding may be indicatory of delayed T2D diagnosis in men versus women with YOD, and could potentially contribute to higher occurrence of retinopathy in men with YOD.

YOD is often defined as diabetes diagnosis before age 40, with some variation in cut-off age, challenging direct comparison.[2] We found a somewhat higher YOD prevalence compared with European population-based studies, most likely explained by our relatively high proportion with non-Western background.[6 18]

A meta-analysis of European primary care data on individuals with T2D reported overall retinopathy prevalence at 25%, ranging from 15% to 35% in the largest European countries.[19] Our finding of 13% retinopathy prevalence may be an underestimate due to relatively poor compliance with recommendations on referral to eye examination and lack of a retinopathy screening program in Norway.[16]

Most studies of complications in YOD, including retinopathy, report from secondary care. Our primary care setting challenges direct comparison, but gives opportunity for richer clinical data than registry-based studies and more representative data than selected hospital-based populations. No population-based registry studies or previous primary care-based studies of YOD and retinopathy were identified. A systematic review and meta-analysis, of mainly hospital-based observational studies, found 8% (OR 0.92 (0.90 to 0.95)) decreased risk of retinopathy for each year older at T2D diagnosis after adjustment for current age, comparable with our finding of 10% decrease per year in a primary care population.[3]

Our observed trend of more frequent retinopathy treatment in YOD compared with later-onset T2D, although a non-significant interaction relating to low power, is in accordance with other studies, indicating that not only overall retinopathy, but also the more severe forms have increased prevalence in YOD.[20]

We did not find that individuals with YOD received less intensive follow-up for retinopathy, the proportion with an eye examination in the last 30 months was similar across all age-at-diagnosis groups. However, we have previously reported that current age below 50 years was related to lower rate of eye examination while more frequent examination rates were seen in those with longer diabetes duration.[16] These potentially opposing effects fit well with individuals with YOD having examination rates comparable to later-onset T2D, as they have both lower age and longer diabetes duration on average.

Our study is in line with previous findings of higher HbA_{1c} in YOD despite more intensive treatment.[11] Evaluating identified mediators, we found that diabetes duration and HbA_{1c}, but not LDL cholesterol and blood pressure, contributed to the increased OR for retinopathy. These findings align with most previous studies.[3 9 21] One study has suggested hypertension, a known risk factor for retinopathy,[22] to be a predictor of retinopathy in YOD,[21] while the roles of lipids and smoking in retinopathy development are less established[23 24] and have not been found to mediate increased risk in YOD.

We have not identified previous studies reporting comparisons of prevalence or severity of retinopathy between men and women with YOD . A systematic review assessing overall retinopathy levels by sex found conflicting results.[25] The reviewers found no relevant studies from Europe or North America, and none that focused on age at diabetes diagnosis. We may therefore be the first to report an excess likelihood of retinopathy in men with YOD unexplained by known mediators. We cannot rule out that the sample size precluded a similar residual effect in women with YOD, but our findings suggest that the impact of YOD on the likelihood of retinopathy may differ by sex.

In men with YOD, treatment rates and prevalence of visual impairment were higher than in women with YOD, and time from T2D diagnosis to first treatment of retinopathy shorter. This is in line with the sex difference in

direct effect of YOD on OR for retinopathy of all severities, substantiating the clinical relevance.

As mentioned above, a possible explanation for the remaining excess likelihood of retinopathy in men with YOD is that diabetes diagnosis may be more commonly delayed in young men than in young women. This would fit with our and others' findings of substantially higher HbA_{1c} at diagnosis in men, particularly when comparing men and women with YOD. If so, the increased retinopathy prevalence in men with YOD could be ascribed to longer exposure to hyperglycemia before diagnosis. This speculation aligns with women visiting their GPs more frequently. This applies particularly in relation to pregnancies, where screening for T2D and gestational diabetes mellitus is recommended, especially in high-risk groups, thus reducing the likelihood of delayed T2D diagnosis.[26] After diabetes diagnosis, men and women seemed to have the same initial response to commencing glucose-lowering treatment and similar development of HbA_{1c} over time, but HbA_{1c} remained higher in men than women.

Our finding of very few adolescents diagnosed with T2D is in line with the low incidence of T2D recorded in the Norwegian Childhood Diabetes Registry[27] and guided this study's focus on onset in young adulthood. T2D in adolescence has previously been suggested to represent a more adverse diabetes phenotype[11] with more insulin resistance, more rapid beta-cell failure[2] and poorer clinical outcomes.[28] However, pathophysiology of T2D in adolescence may differ from that of onset in young adulthood, specifically relating to ongoing or completed puberty.

Strengths and limitations

This is one of very few studies from primary care to assess prevalence and potential sex differences of YOD and retinopathy. The ROSA 4 dataset is considered to be representative for the population with T2D in Norwegian general practice.[29] Compared with most registry-based datasets, these data from GPs' EMRs provide more clinical details. To reduce the risk of misclassification between T1D and T2D, diagnosis of diabetes was manually validated, especially in individuals with younger age at diagnosis.

Although a cross-sectional design was used, long-term relationships between individuals and their GPs documented in the EMRs have allowed us to capture data for relevant variables dating years and even decades back. We had access to repeated HbA_{1c} measurements allowing for detailed analyses of development of hyperglycemia from the time of diabetes diagnosis. Prior to analysis, we developed a directed acyclic graph to identify potential confounders and mediators. Linkage to data from Statistics Norway allowed adjustment for important demographic confounders. Further, we performed multiple imputations of missing data to reduce potential bias, and we also report results of complete case analyses. As almost all individuals with T2D in Norway are cared for in general practice, our results may be representative for other countries where T2D care is mainly a responsibility of primary care.

In a real-life dataset, we had to expect a relatively large proportion of missing values for some variables, causing bias from lack of examination or reporting. It is previously reported from ROSA 4 that adherence to microvascular screening recommendations in Norwegian general practice is incomplete, with only 60% having recorded a recommended biennial eye exam. This means data on retinopathy status were missing in 40%.[16] One explanation may be that not all fundus examinations are recorded in GPs' EMRs, especially when performed by optometrists without referral.[30] The lack of a national eye screening program in Norwegian diabetes care may also have contributed. The groups with known and unknown retinopathy status remained comparable, lending support to missing at random, a prerequisite for imputation. That the imputed datasets gave similar results to complete case regression analyses, increases the confidence in our assumption and findings.

For our primary outcome retinopathy, we lacked data on grading of severity. However, data on treatment of retinopathy and visual impairment gave an indication of the prevalence of symptomatic and more severe disease. With only 1.7% of the ROSA 4 population having undergone retinopathy treatment, the power to detect group differences was too small for analyses beyond simple descriptives.

Although the predominantly cross-sectional design precluded us from measuring incidence of our primary outcome and drawing firm conclusions on causality, our main findings honor Bradford Hill's criteria of strong association and consistency in findings.[31] Assuming that YOD (exposure) precedes the development of retinopathy (outcome) the Bradford Hill's criterion of temporality is also met.

Despite the mainly cross-sectional design, longitudinal data series of HbA_{1c} levels were available. Unfortunately, these could not be linked to the imputed dataset, hence only the latest HbA_{1c}-measurement was analyzed as a possible mediator for the likelihood of retinopathy by age at diabetes diagnosis and sex. In the longitudinal analyses, HbA_{1c} differed substantially more between men and women with YOD at diagnosis than at all later time points. This may partly explain the higher likelihood of retinopathy in men with YOD. The inclusion of only the later HbA_{1c} measurement from the cross-sectional dataset in the logistic regression analyses may have precluded finding a significant interaction between sex and HbA_{1c} in the mediation of increased OR for retinopathy in YOD.

Although data were collected in 2015 and may not reflect more recent trends in disease prevalence, we consider our analyses of associations between exposures and outcomes to be robust and most likely still valid.

Implications for clinicians

Our results indicate that earlier T2D diagnosis and stronger adherence to retinopathy screening could

alleviate some of the excess retinopathy seen in YOD. We recommend an increased awareness of undiagnosed T2D and an active case-finding strategy, particularly in young men with known risk factors for T2D. After diabetes diagnosis, close monitoring, treatment and prompt referral to eye examination are warranted. Finally, clinicians should be aware of the paradox of generally higher glycemic levels in YOD despite more abundant treatmentwith antidiabetic medication, indicating a need for more focus on barriers against patient life style changes, drug adherence and diabetes self-care.

Implications for research

Larger longitudinal studies in a population-based setting, including primary care data with more detailed retinopathy outcome measures, are required for more knowledge on the consequences of increased retinopathy prevalence in YOD. Further studies are also required to assess the mechanisms underlying the unexplained excess likelihood of retinopathy in men with YOD and the inadequate diabetes control in YOD despite higher intensity of glucose-lowering treatment.

CONCLUSION

Ten percent of men and women in Norwegian general practice with T2D were diagnosed before age 40. YOD is associated with higher levels of HbA_{1c} and a more than doubled likelihood of retinopathy. This excess likelihood, probably mediated by a higher glycemic load over time, remains partly unexplained in men with YOD.

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Patient consent for publication Not applicable.

Ethics approval To obtain real-life data and avoid selection bias, ROSA 4 was approved for collection with consent from GPs and without consent from patients by the Regional Ethics Committee West (2014/1374 REK Vest). The Norwegian Diabetes Association informed individuals with diabetes of the possibility to withdraw from the study.

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