UNIVERSITÀ DEGLI STUDI DI TORINO

ESTIMATING THE DELAY BETWEEN ONSET AND DIAGNOSIS OF TYPE 2 DIABETES FROM THE TIME-COURSE OF RETINOPATHY PREVALENCE

Running title: Undiagnosed diabetes and prevalence of retinopathy

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ABSTRACT

Objective: Longer than 10 years has been estimated to lapse between onset and diagnosis of type 2 diabetes, by correlating known diabetes duration with prevalence of retinopathy. However, such calculations assumed a linear model, included stages of retinopathy non specific to diabetes and allowed 5 years for retinopathy to appear after diabetes. We calculated the length of undiagnosed type 2 diabetes in outpatients screened for retinopathy in a hospital-based diabetes clinic after correcting these assumptions.

Research Design and Methods: Diabetic patients (n=12,074; 35,545 fundus examinations) were stratified into Younger-Onset (YO, age at onset <30) or Older-Onset (OO, ≥30), insulin treated (IT) or not (NIT), and with mild/more severe (AnyDR) or moderate/more severe retinopathy (ModDR). The best-fitting equation correlating known OO-NIT duration with prevalence of ModDR was used to extrapolate time from appearance of retinopathy to diagnosis of type 2 diabetes. Time for retinopathy development after diabetes was calculated from the equation correlating duration of YO-IT with appearance of ModDR.

Results: There were 1,719 OO-NIT with AnyDR and 685 with ModDR, 756 YO-IT with AnyDR and 385 with ModDR. A linear model showed ModDR appearing 2.66 years before diagnosis of OO-NIT. A quadratic model suggested that ModDR appeared 3.29 years after YO-IT. The resulting estimate was (2.66+3.29=) 6.05 years between onset and diagnosis of diabetes, against 13.36 using standard criteria.

Conclusions: Using best fitting models and stratification by glucose-lowering treatment and severity of retinopathy substantially lowers the estimated length of undiagnosed type 2 diabetes.

Type 2 diabetes is defined as a chronic condition characterised by increased blood glucose levels resulting from a progressive insulin secretory defect on the background of insulin resistance (1). About 15% of adults in the UK have impaired glucose regulation (2) and 5-12% of them progress to type 2 diabetes each year (3). Because of this gradual, asymptomatic onset, type 2 diabetes may remain undiagnosed for years, during which micro- and macrovascular complications progress unchecked, so that the prevalence of diabetic retinopathy (DR) at diagnosis ranges from 10 to 37% in different reports on Caucasian populations (4-7). The latter observation prompted some authors to estimate the time elapsing from onset of diabetes to its clinical diagnosis through the correlation between known duration of type 2 diabetes and prevalence of DR. Assuming that such correlation is linear, and that DR appears after diabetes, extrapolating the regression line before the time of diagnosis yielded estimated lengths of unknown retinopathy duration between 4 and 9 years (6,7). Since it was assumed that DR needs another 5 years to appear after onset of diabetes, the total estimated duration of unrecognised type 2 diabetes was extended to well beyond 10 years.

However, there were limitations in those studies: 1) the correlations between diabetes duration and prevalence of retinopathy were calculated including mild and very mild lesions (isolated microaneurysms, haemorrhages or cotton wool spots) which were later shown detectable in up to 10% of the general non-diabetic, non-hypertensive population and in people with pre-diabetic states (5,8-11); 2) the linearity of the correlation has been questioned recently (7); 3) the plausibility of such a long time of undiagnosed diabetes is also questionable, at least in countries with structured health care systems in which blood glucose levels are supposedly measured more often than every 10 years, for routine or elective purposes.

In this paper, we used prospective data collected while screening for DR to estimate the duration of undiagnosed type 2 diabetes in a large ambulatory patient population in a hospital-based diabetes clinic. In particular, we were able to 1) discriminate patients with any retinopathy from those with moderate or more severe DR, which is more specific to, and more likely to develop after the onset of, diabetes; 2) apply the best fitting models, linear or more complex, to the correlations between known duration and different severities of DR; 3) verify such correlations in patients with type 1 diabetes, in whom the date of onset is well defined.

RESEARCH DESIGN AND METHODS

The data of 35,545 screening episodes performed in 12,074 patients (6,751 males [55.91%] and 5,323 females [44.09%]) between 1/1/1991 and 31/12/2010 were evaluated. The persons subjected

to screening were almost totally of European origin, with few patients of African, Asian or South American descent included in the latest years. Data were collected prospectively using a dedicated software, SEE (Save Eyes in Europe) (Elilan, Turin, Italy), specifically designed to record episodes according to the 1990 European Working Party screening protocol (12). All study participants gave their informed consent and the investigations were carried out in accordance with the Declaration of Helsinki.

Details of the retinal screening procedure, grading and quality assurance in this population were described previously (13). In brief, screening was by colour retinal photographs of two 45° retinal fields for each eye, one centered on the macula and the other nasal to the optic disc, taken by trained medical or nursing personnel and graded by diabetes specialists according to the 1990 European Working Party protocol (14).

Patient classification

Patients were classified as having any retinopathy (AnyDR) if they had mild lesions (microaneurysms and/or isolated larger haemorrhages and/or isolated cotton wool spots) equivalent to ETDRS level ≤20 (15), or worse. Those with DR equivalent to ETDRS level >20 or worse (moderate non proliferative, pre-proliferative, proliferative, photocoagulated DR, advanced diabetic eye disease with or without macular involvement), were classified as having moderate non proliferative DR or worse (ModDR). For patient classification, DR severity in the worst eye was considered.

The patients were divided into younger-onset (YO) if age at diagnosis of diabetes was <30 and older-onset (OO) if it was ≥30, and further stratified into insulin-treated (IT), either alone or with oral agents, and non insulin treated (NIT), i.e. on diet alone or with oral agents. Age at diagnosis was self-reported, and checked on medical records whenever possible. There were 7,298 OO-NIT (58.4% males, age 63.1±10.3, known diabetes duration 6.4±7.4), 2,945 OO-IT (52.9%, 63.1±11.8, 13.3±10.1), 1,725 YO-IT (50.7%, 30.1±14.6, 15.2±11.2), and 106 YO-NIT (50.9%, 40.0±16.0, 17.4±14.8). Because of its limited size, the latter group was not further considered.

Calculations.

Relationships between known duration of diabetes and prevalence of AnyDR or ModDR were evaluated separately for the OO-NIT, OO-IT, and YO-IT. Patients with more than one follow up screening were included as separate observations with the severity of retinopathy observed at each different time point. The nil prevalence of retinopathy for each group was estimated using as first model a simple linear regression analysis (prevalence = a+b*known duration of diabetes). Then a quadratic term, evaluated by the Likelihood ratio test (LR), was introduced in the model. Akaike

Information Criterion (AIC) and Coefficient of Determination (R^2) were used to choose the best fitting model. For the YO-IT with AnyDR a logistic model was fitted, as neither linear nor quadratic models fitted adequately.

The time from onset of retinopathy to clinical diagnosis of diabetes was calculated as point estimates by extrapolating the intercept of the best fitting regression line with the horizontal axis.

RESULTS

Prevalence of AnyDR and ModDR increased up to 20 years known duration, then tended to plateau (data not shown). Hence, further calculations were performed taking into account the first 20 years known duration of diabetes. Table 1 summarizes the best fits estimated for the different models.

Figure 1 shows the regression lines between known duration of diabetes and prevalence of AnyDR in the OO-NIT, OO-IT and YO-IT. Both linear (1a) and quadratic (1b) models are shown for AnyDR and OO-NIT, confirming that a quadratic model provides the best fit. The best fits for AnyDR and OO-IT and YO-IT were provided by linear (1c) and logistic (1d) equations, respectively. The intercepts on the horizontal axis for AnyDR were: – 8.46 years for OO-NIT (linear model, Fig. 1a) and –3.89 years (quadratic model, Fig. 1b), –4.27 years for OO-IT (quadratic model, Fig. 1c). In the case of YO-IT (Fig. 1d) the intercept was estimated as not different from zero.

Figures 2 a-c show that the best fits between known duration of diabetes and prevalence of ModDR in the OO-NIT, OO-IT and YO-IT were provided by linear, quadratic and quadratic equations, respectively. The resulting intercepts between known duration and ModDR were at –2.66 years for OO-NIT, –3.36 years for OO-IT and +3.29 years for the YO-IT.

Since we and others previously demonstrated that appearance of DR is delayed when onset of diabetes is in pre-pubertal years (16,17), estimations in the YO-IT group were repeated for a subgroup of patients (n=829) in whom age at onset had been >12 if males (n=415) and >11 if females (n=414). The resulting best fit was also a quadratic equation with intercept on the x axis at 1.73 years (Table 1 and Fig. 2d).

The above data suggest that AnyDR had started to develop 3.89 years before clinical diagnosis of diabetes in the OO-NIT, whereas data in the YO-IT do not allow to reliably estimate time from onset of diabetes to start of AnyDR, making it impossible to work out an estimate for unknown

duration of type 2 diabetes when using AnyDR as a model.

ModDR started to develop in the OO-NIT an estimated 2.66 years before diagnosis of type 2 diabetes, and 3.29 years after onset of diabetes in the YO-IT, or 1.73 years if only patients with diabetes onset after puberty are considered. The OO-IT behaved somewhat in between OO-NIT and YO-IT (Table 2 and Figures 1, 2), suggesting that this group may include individuals with later onset (after age 30) type 1 diabetes. Consequently, this group was not further considered.

Assuming that, in the YO-IT, time to appearance of ModDR indicates the time elapsing from onset of diabetes to start of diabetic retinopathy, the total time from onset to diagnosis of type 2 diabetes was estimated at 2.66 + 3.29 = 5.95 years. Restricting the model to data from patients with post-pubertal onset T1DM brought the estimate down to 2.66 + 1.73 = 4.39 years.

CONCLUSIONS

This paper suggests that type 2 diabetes may arise 4-6 years before a clinical diagnosis is reached, much less than previous estimates putting this interval at longer than 10 years (6,7,18,19). Applying previous approaches in the literature to our population, ie a linear model with AnyDR as indicator and assuming 5 years for retinopathy to appear, would also yield an 8.36 + 5 = 13.36 year estimated interval of undiagnosed diabetes.

The first attempt to estimate the interval from onset to clinical diagnosis of type 2 diabetes was published by Harris et al. (6) who calculated the weighted linear regressions between known duration and prevalence of DR in two different white populations, one residing in Wisconsin and the other in Australia, and suggested that DR starts to develop 6.5 (95% CI 4.1-9.9) and 4.2 (2.1-7.4) years before diagnosis, respectively. To these numbers, an estimated 5 years for retinopathy to develop after the onset of type 2 diabetes was added, bringing the total time of undiagnosed diabetes to 9-12 years. The two populations had different characteristics, both in the definitions used to assign a diagnosis of Non Insulin Dependent Diabetes (NIDDM) and in the methods used to detect retinopathy. In addition, patients were lumped together, whether they were on insulin or not, and any severity of retinopathy was considered. The Wisconsin cohort included patients either on insulin treatment or not at the time of study and defined NIDDM on the basis of age at diagnosis ≥30 and no insulin treatment for at least 2 years thereafter. Their results are in between the estimates we reached for the OO-NIT and OO-IT using a linear model (8.46 and 4.27 years, respectively).

Using a similar approach in a South Indian outpatient population, Ramachandran et al. (18)

estimated 4.1 years preceding diagnosis of NIDDM, defined by an oral glucose load. Any retinopathy, assessed from detailed dilated eye examination by an ophthalmologist, was plotted against known duration, but the overall prevalence of DR was lower than in previous reports. In another study of Egyptian adults (19), using the same model, the lag time between onset of diabetic retinopathy and clinical diagnosis of NIDDM was 2.6 years which, by adding an assumed 5 years for retinopathy to appear after onset of diabetes, brought the total estimated time of unknown diabetes to 7.6 years.

Finally, in a selected population with type 2 diabetes in Tayside, Ellis et al (7) extrapolated 5.77 (4.6-7.0) years from beginning of DR to clinical diagnosis of type 2 diabetes, to which the customary 5 year time to develop retinopathy from onset of diabetes was added. The authors however, questioned the linearity of the correlation, citing the by then established presence of minimal retinal lesions in people without diabetes (11) and the possibility of a glycaemic threshold below which retinopathy may start to appear and that might differ from current diagnostic criteria for diabetes.

The point was raised by other investigators, questioning whether current diagnostic criteria are truly indicative of a threshold glycaemic level below which microvascular complications do not develop. These criteria are based upon 3 reports suggesting that 7.0 mmol/l (126 mg/dl) represent the glycaemic threshold below which DR will not appear (20) but the methodology to detect retinopathy in those papers has been questioned later (7,11). Observations in Pima Indians (21) and from the Diabetes Prevention Programme (DPP) showed that retinopathy may appear in people with impaired glucose tolerance (22). Wong et al examined data from three large cross-sectional adult populations, the Blue Mountains Eye Study in Australia (n=3162), the Australian Diabetes, Obesity and Lifestyle Study (n=2182) and the Multi-Ethnic Study of Atherosclerosis in the US (n=6079), and could not confirm the notion of a glycaemic threshold (11).

In this paper, the problem was addressed by calculating not only the regressions between known duration of type 2 diabetes and any retinopathy, which would include carriers of less specific minimal retinal lesions, possibly independent of diabetes (5,8-11), but also those between known duration and moderate or worse DR, which is more specific to diabetes (11). The latter model yielded a shorter interval from intercept on the x-axis to time zero, -2.66 years for OO-NIT patients. Data collected in the YO-IT patients suggest 3.29 years for ModDR to develop after onset of diabetes, resulting in an overall 6 year estimated interval of undiagnosed diabetes, which is shorter than previous estimates. Including only patients with post-pubertal onset type 1 diabetes, in whom

retinopathy may progress more rapidly (16,17), further reduced the estimate to 4.39 years. Progressively increasing prevalence of DR was observed within the first 20 years of known diabetes duration, followed by a plateau, suggesting that a survivor effect may take place thereafter, as DR is an established independent predictor of cardiovascular mortality (23). Hence, similarly to previous studies in the literature, we limited our observation time to the first 20 years.

Strengths of this paper include a large population database obtained prospectively from a screening programme which uses a defined consensus protocol (13,14) and a software that forces operators to collect all required information without missing data. Grading criteria allowed to discriminate mild from more severe DR, on a scale compatible with the ETDRS classification (15). Finally, information on glucose-lowering therapy at the time of screening allowed to separate older onset patients into those who were not on insulin, a supposedly "pure" population of type 2 diabetes, and an equally virtually "clean" group of type 1 diabetes patients, younger onset on insulin, in whom certainty about date of diabetes onset provided information on the incidence and progression rates of DR. In particular, the curves of cumulative prevalence of non proliferative and pre-proliferative DR (data not shown) were virtually superimposable with those reported in EURODIAB, a survey of complications in patients with T1DM across Europe (24). The OO-IT were not included in these calculations because they may include a case mix of patients with both late onset type 1 diabetes and long standing type 2 diabetes. However, data from Table 1 show that their inclusion would have resulted in even shorter estimates for unknown diabetes duration.

Weaknesses include lack of information on HbA1c and blood pressure, two major determinants of DR incidence and progression, a problem shared with other large screening programmes (25). In addition, the patients in this study were subjected to screening for DR over a 20 year period and their type 2 diabetes had been diagnosed using current criteria at different times. Also, retinal photography was by 2-field non-stereo 45° images, rather than standard ETDRS 7-field 30° stereos (15). However, our photographic protocol was based upon the EURODIAB procedure, which had been previously validated and found to perform as well as the ETDRS in detecting mild and moderately severe DR (26). In any event, figures for prevalence of DR at diagnosis in our different subgroups are consistent with previous data in the literature, suggesting that our results can be generalised at least to other white populations. Finally, we extrapolated data obtained in patients with type 1 diabetes, in whom the date of onset is certain, to estimate time from onset of diabetes to appearance of retinopathy in type 2 because there are no recent data on the appearance of moderate or more severe retinopathy in non insulin treated patients. The 5 year time for retinopathy to develop, as used in the literature, derived from prospective observation studies of mixed

populations of insulin-treated and non insulin-treated patients with NIDDM in Wisconsin and the UK (6) and included any mild lesion, not necessarily specific for diabetic retinopathy. Our approach may have a problem because there are no direct comparisons of the incidence rates of moderate/more severe retinopathy in type 1 and type 2 diabetes. If anything, our own data suggest that the cumulative prevalences of ModDR in the OO-NIT (Fig. 2a) and post-pubertal YO-IT (Fig. 2d) are similar in slope, although described by linear and quadratic functions, respectively. A possible interpretation is that, while metabolic control is usually worse in type 1 diabetes in the early years, age and higher blood pressure could contribute to more rapid progression of retinopathy in type 2, resulting in overall similar rates of development in the two conditions.

In conclusion, this paper suggests that metabolic abnormalities may precede clinical diagnosis of non insulin treated type 2 diabetes by 4 to 6 years, which is much less than previous estimates. Whether such metabolic abnormalities coincide with current diagnostic criteria for type 2 diabetes remains to be established. That about 15% of the adult population may suffer from impaired glucose regulation without having full-blown type 2 diabetes (2) and that impaired glucose tolerance is associated with increased risk for DR (19,20) suggests that part of those "hidden" years may be spent in a pre-diabetic state (1), accounting at least in part for delayed and incomplete diagnoses of diabetes. Sorting out these issues will provide more solid basis upon which to decide on the feasibility and opportunity of screening programmes for the early detection of type 2 diabetes (27).

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Table 1. Estimated best fits for the correlations between prevalence of retinopathy and known duration of diabetes according to the Akaike Information Criterion (AIC), Coefficient of Determination (R^2) and Likelihood Ratio (LR) test

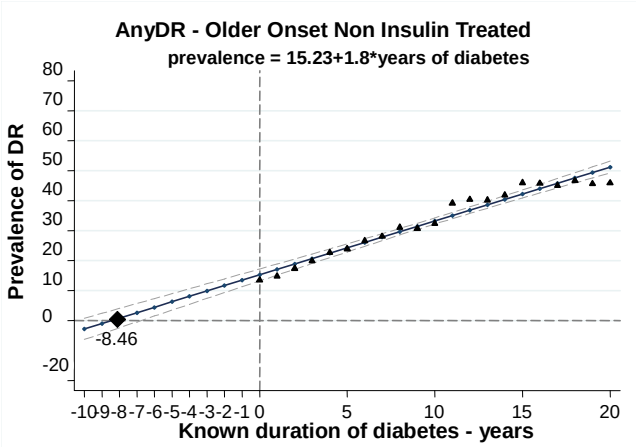
(OO-NIT=Older Onset – Non Insulin Treated; OO-IT=Older-Onset – Insulin Treated; YO-IT=Younger Onset – Insulin Treated; YO-NIT=Younger-Onset – Non Insulin Treated)

AnyDR	**Model**	**AIC**	**R^2**	**Intercept on x axis (yrs)**	**LR test**
OO-NIT	Linear	98.43	0.96	-8.46	
	Quadratic	82.82	0.98	-3.89	<0.0001
OO-IT	Linear	119.3	0.97	-4.27	
	Quadratic	118.8	0.97	-2.84	0.12
YO-IT	Linear	138.4	0.94	1.6	
	Quadratic	137.8	0.94	1.0	0.11
	Logistic	116.7	0.99	0	Not applicable
YO-IT post-pubertal	Linear	144.3	0.93	0.28	
	Quadratic	144.9	0.93	0.89	0.25
	Logistic	127.5	0.98	0	Not applicable
ModDR					
OO-NIT	Linear	91.7	0.94	-2.66	
	Quadratic	93.2	0.94	-3.85	0.46
OO-IT	Linear	119.3	0.97	-0.74	
	Quadratic	114.1	0.98	-3.36	0.007
YO-IT	Linear	141.5	0.85	3.79	
	Quadratic	124.4	0.94	3.29	<0.0001
YO-IT post-pubertal	Linear	124.3	0.86	2.85	
	Quadratic	120.5	0.90	1.73	0.02

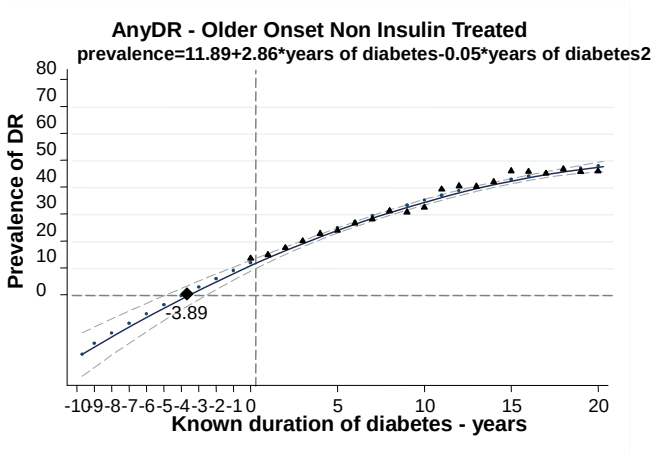
Fig. 1. Best fits between known duration of diabetes and prevalence of AnyDR in the OO-NIT (1a – linear model; 1b – quadratic model), OO-IT (1c – linear model) and YO-IT patients (1d – logistic model).

(OO-NIT=Older Onset – Non Insulin Treated; OO-IT=Older-Onset – Insulin Treated; YO-IT=Younger Onset – Insulin Treated; YO-NIT=Younger-Onset – Non Insulin Treated)

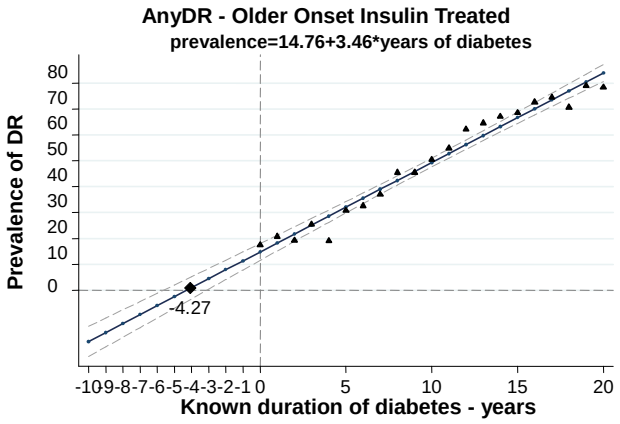
a)



b)



c)



d)

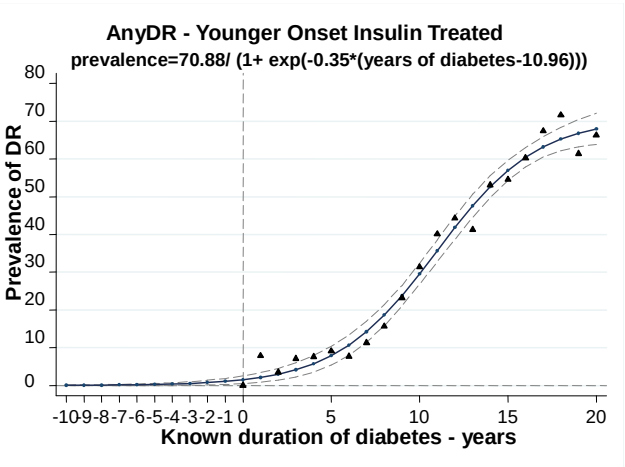
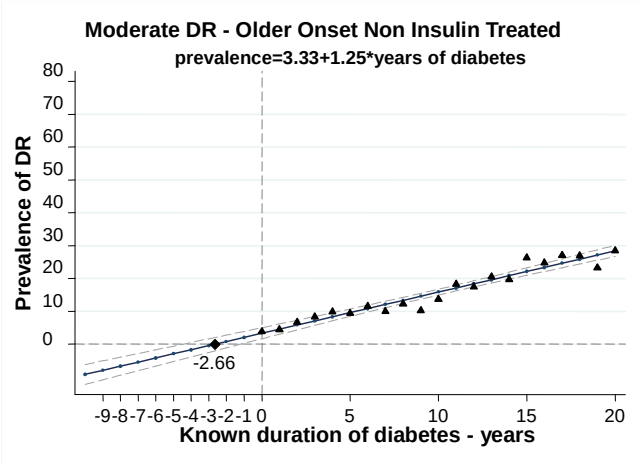


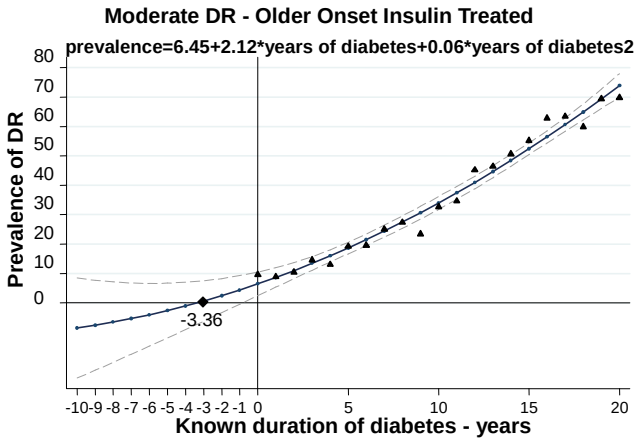
Fig. 2. Best fits between known duration of diabetes and prevalence of ModDR in the OO-NIT (2a), OO-IT (2b), all YO-IT patients (2c) and patients with post-pubertal onset YO-IT (2d).

(OO-NIT=Older Onset – Non Insulin Treated; OO-IT=Older-Onset – Insulin Treated; YO-IT=Younger Onset – Insulin Treated; YO-NIT=Younger-Onset – Non Insulin Treated)

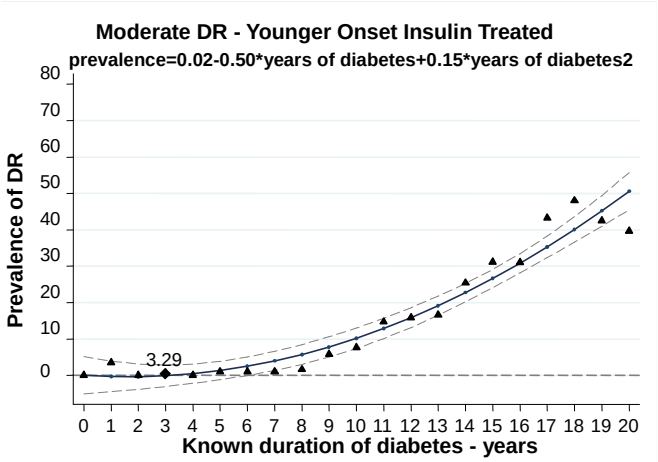
a)



b)



c)



d)