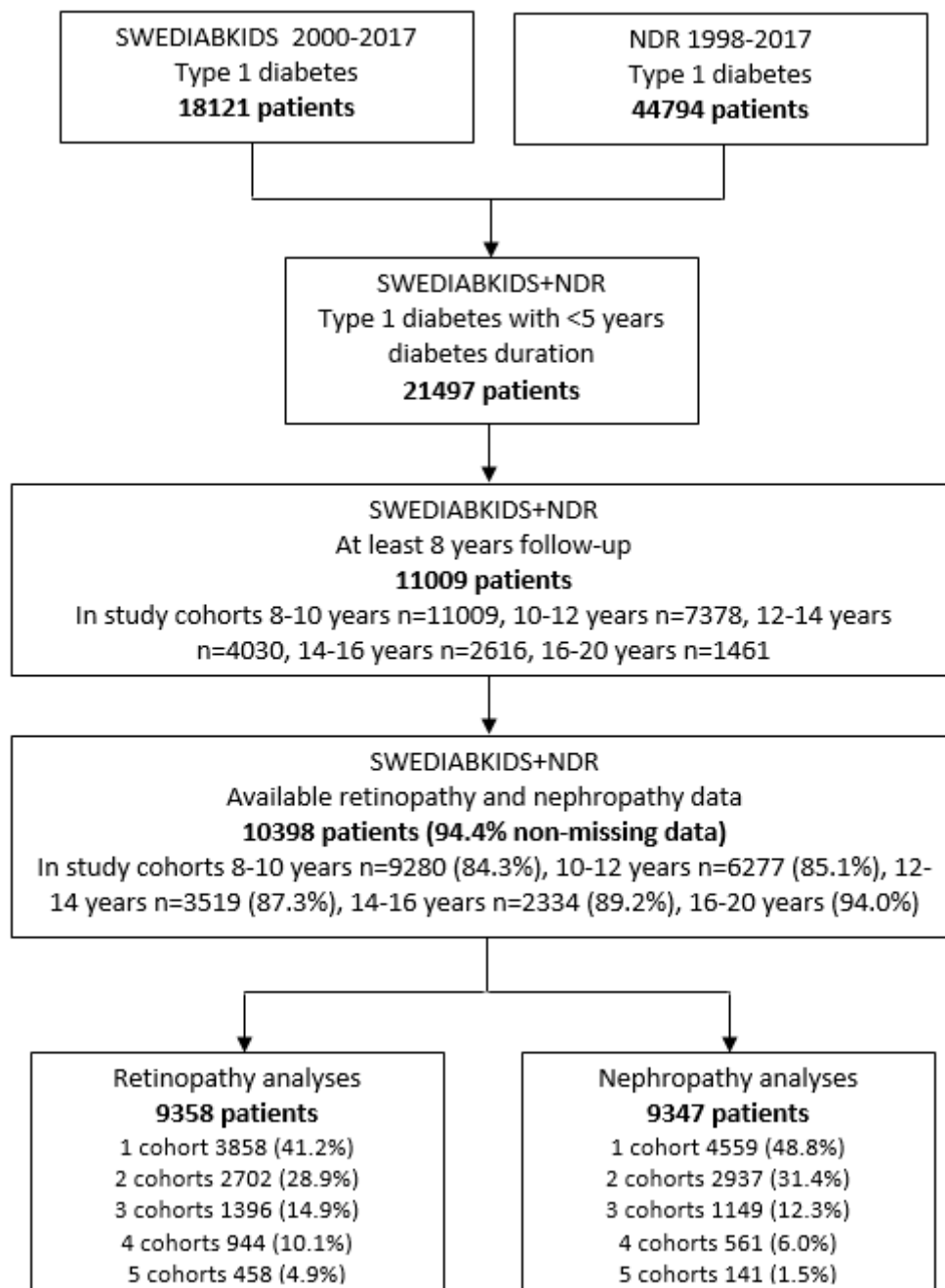# HbA$_{1c}$ level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes: Swedish population based cohort study

Lind M, Pivodic A, Svensson A-M, Ólafsdóttir AF, Wedel H, Ludvigsson J.

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Supplemental Figure 1. Study cohorts

Legend Figure 1. Flow-chart of various steps of included patients in the analyses.

Supplemental Table 1. Patient characteristics for overall cohort and for patients with HbA1c AUC <48 mmol/mol.

Variable		HbA1c AUC <48 mmol/mol	
	All patients (n=10398)	**No PDR/Laser or macroalbuminuria (n=769)**	**PDR/Laser or macroalbuminuria any time (n=12)**
Diabetes onset year	2003 (4) 2004 (1993; 2009) n=10398	2003 (4) 2004 (1993; 2009) n=769	2004 (4) 2003 (1999; 2009) n=12
Age at first visit	14.7 (8.1) 13.0 (0.0; 34.0) n=10398	20.2 (7.4) 21.0 (0.9; 34.0) n=769	22.7 (8.2) 23.5 (2.1; 33.0) n=12
HbA1c AUC for longest follow-up	63.4 (11.7) 62.3 (29.1; 120.9) n=10398	43.9 (3.8) 45.1 (29.1; 48.0) n=769	45.1 (3.0) 45.7 (38.8; 47.9) n=12
SBP mean for longest follow-up	116.3 (8.9) 115.9 (80.0; 175.0) n=10372	117.9 (9.3) 117.6 (92.0; 166.7) n=767	119.6 (7.2) 120.4 (103.0; 131.2) n=12
DBP mean for longest follow-up	69.8 (6.0) 69.6 (47.1; 105.0) n=10372	70.5 (5.9) 70.4 (52.0; 94.4) n=767	72.0 (7.0) 71.3 (59.8; 84.9) n=12
BMI mean for longest follow-up	22.7 (4.1) 22.2 (13.2; 48.4) n=10362	23.1 (3.6) 22.9 (13.9; 39.9) n=762	21.9 (3.2) 21.9 (16.9; 27.8) n=12
HDL mean for longest follow-up	1.52 (0.38) 1.48 (0.40; 5.90) n=9171	1.55 (0.37) 1.50 (0.70; 4.40) n=712	1.61 (0.51) 1.56 (0.78; 2.30) n=11
LDL mean for longest follow-up	2.52 (0.68) 2.45 (-0.36; 8.94) n=9156	2.40 (0.62) 2.36 (0.80; 4.76) n=708	2.05 (0.33) 1.87 (1.72; 2.54) n=11
Cholesterol mean for longest follow-up	4.48 (0.78) 4.41 (2.20; 11.00) n=9370	4.32 (0.71) 4.29 (2.25; 7.33) n=717	4.11 (0.45) 4.17 (3.55; 4.80) n=11
Triglycerides mean for longest follow-up	1.07 (0.68) 0.90 (0.20; 18.06) n=8920	0.881 (0.420) 0.776 (0.200; 3.640) n=708	0.928 (0.360) 0.900 (0.400; 1.600) n=11
Smoking max for longest follow-up			
No	6837 (77.3%)	625 (88.7%)	11 (100.0%)
Yes	2010 (22.7%)	80 (11.3%)	0 (0.0%)
For categorical variables n (%) is presented. For continuous variables Mean (SD) / Median (Min; Max) / n= is presented.			

Supplemental Table 2.1 Number and percent of retinopathy endpoints for each time period and the effect of HbA1c AUC categories and HbA1c AUC per 10 mmol/mol increase on endpoints by using unadjusted and adjusted logistic regression.

	Any retinopathy vs None			PPDR/PDR/Laser vs None/Simplex			PDR/Laser vs None/Simplex/PPDR		
	n (%) events	Unadjusted	Adjusted**	n (%) events	Unadjusted	Adjusted**	n (%) events	Unadjusted	Adjusted*
Follow-up 8-10 years from onset (n=8049)									
<48	55 (8.8%)	0.90 (0.63-1.29)	0.83 (0.56-1.23)	6 (1.0%)	4.21 (0.85-20.93)	2.88 (0.58-14.40)	5 (0.8%)	3.50 (0.68-18.12)	2.55 (0.49-13.27)
48-52	84 (9.6%)	1.00	1.00	2 (0.2%)	1.00	1.00	2 (0.2%)	1.00	1.00
53-57	164 (11.6%)	1.23 (0.93-1.62)	1.47 (1.06-2.04)	3 (0.2%)	0.92 (0.15-5.54)	0.78 (0.11-5.59)	2 (0.1%)	0.62 (0.09-4.37)	0.79 (0.11-5.64)
58-70	569 (16.6%)	1.87 (1.47-2.38)	2.11 (1.58-2.82)	24 (0.7%)	3.07 (0.72-13.02)	3.92 (0.91-16.91)	7 (0.2%)	0.89 (0.18-4.30)	1.34 (0.28-6.50)
>70	491 (28.6%)	3.75 (2.93-4.80) c=0.63	3.55 (2.63-4.80)	35 (2.0%)	9.04 (2.17-37.65) c=0.69	7.75 (1.78-33.72)	7 (0.4%)	1.78 (0.37-8.58) c=0.64	2.32 (0.48-11.26)
HbA1c AUC (OR per 10 units)		1.55 (1.47-1.63) p=<0.0001 c=0.64 (0.62-0.66)	1.51 (1.42-1.62) p=<0.0001		1.92 (1.64-2.24) p=<0.0001 c=0.70 (0.63-0.77)	1.78 (1.46-2.16) p=<0.0001		1.24 (0.89-1.73) c=0.51	1.31 (0.97-1.77) p=0.073
Follow-up 10-11 years from onset (n=5324)									
<48	18 (6.6%)	0.44 (0.26-0.76)	0.43 (0.24-0.76)	2 (0.7%)	1.81 (0.25-12.92)	2.85 (0.26-31.69)	1 (0.4%)	1.81 (0.11-29.01)	1.44 (0.09-23.28)
48-52	68 (13.9%)	1.00	1.00	2 (0.4%)	1.00	1.00	1 (0.2%)	1.00	1.00
53-57	127 (14.8%)	1.08 (0.78-1.48)	1.00 (0.69-1.44)	3 (0.3%)	0.85 (0.14-5.13)	1.56 (0.14-17.35)	3 (0.3%)	1.71 (0.18-16.51)	2.11 (0.22-20.47)
58-70	523 (21.7%)	1.72 (1.31-2.26)	1.71 (1.24-2.36)	16 (0.7%)	1.63 (0.37-7.11)	4.94 (0.64-38.06)	5 (0.2%)	1.02 (0.12-8.71)	1.40 (0.16-12.23)
>70	483 (37.2%)	3.67 (2.77-4.85) c=0.64	3.18 (2.28-4.42)	35 (2.7%)	6.75 (1.62-28.16) c=0.70	11.94 (1.57-91.04)	13 (1.0%)	4.94 (0.64-37.84) c=0.68	5.95 (0.77-46.21)
HbA1c AUC (OR per 10 units)		1.75 (1.64-1.86) p=<0.0001 c=0.66 (0.64-0.68)	1.67 (1.54-1.80) p=<0.0001		2.42 (2.01-2.91) p=<0.0001 c=0.75 (0.67-0.83)	2.28 (1.82-2.85) p=<0.0001		2.17 (1.65-2.86) p=<0.0001 c=0.69 (0.55-0.83)	2.07 (1.59-2.70) p=<0.0001
Follow-up 12-13 years from onset (n=3044)									
<48	6 (12.2%)	0.73 (0.28-1.86)	0.55 (0.19-1.55)	0 (0.0%)	3.77 (0.07-197.20)F		0 (0.0%)	3.77 (0.07-197.20)F	
48-52	30 (16.1%)	1.00	1.00	0 (0.0%)	1.00		0 (0.0%)	1.00	
53-57	77 (17.7%)	1.12 (0.71-1.78)	1.11 (0.65-1.87)	2 (0.5%)	2.16 (0.10-45.46)F		1 (0.2%)	1.29 (0.05-32.06)F	
58-70	454 (29.6%)	2.19 (1.46-3.28)	1.95 (1.24-3.07)	19 (1.2%)	4.80 (0.29-80.41)F		4 (0.3%)	1.10 (0.06-20.60)F	
>70	411 (48.9%)	4.97 (3.29-7.52) c=0.64	3.61 (2.26-5.78)	57 (6.8%)	27.34 (1.67-447.71)F c=0.75		20 (2.4%)	9.31 (0.56-155.76)F c=0.77	
HbA1c AUC (OR per 10 units)		1.89 (1.74-2.05) p=<0.0001 c=0.67 (0.65-0.69)	1.72 (1.55-1.91) p=<0.0001		2.96 (2.45-3.58) p=<0.0001 c=0.82 (0.77-0.87)	2.83 (2.20-3.65) p=<0.0001		3.69 (2.72-5.02) p=<0.0001 c=0.86 (0.78-0.94)	3.09 (2.24-4.25) p=<0.0001
Follow-up 14-15 years from onset (n=1927)									
<48	2 (10.0%)	0.55 (0.12-2.59)	0.53 (0.11-2.68)	0 (0.0%)	4.95 (0.09-272.41) F		0 (0.0%)	4.95 (0.09-272.40)F	
48-52	17 (16.8%)	1.00	1.00	0 (0.0%)	1.00		0 (0.0%)	1.00	
53-57	60 (24.6%)	1.61 (0.89-2.93)	1.70 (0.87-3.32)	2 (0.8%)	2.09 (0.10-44.58F		1 (0.4%)	1.25 (0.05-31.38)F	
58-70	352 (35.8%)	2.76 (1.61-4.72)	2.84 (1.56-5.16)	12 (1.2%)	2.61 (0.15-45.05) F		2 (0.2%)	0.52 (0.02-10.98)F	

	Any retinopathy vs None			PPDR/PDR/Laser vs None/Simplex			PDR/Laser vs None/Simplex/PPDR		
	n (%) events	Unadjusted	Adjusted**	n (%) events	Unadjusted	Adjusted**	n (%) events	Unadjusted	Adjusted*
>70	352 (60.8%)	7.66 (4.43-13.24) c=0.66	6.61 (3.57-12.24)	59 (10.2%)	23.21 (1.40-383.63) F c=0.77		23 (4.0%)	8.57 (0.51-144.21)F c=0.80	
HbA1c AUC (OR per 10 units)		2.08 (1.86-2.32) p=<0.0001 c=0.69 (0.67-0.71)	1.91 (1.67-2.18) p=<0.0001		3.18 (2.57-3.93) p=<0.0001 c=0.83 (0.78-0.88)	2.69 (2.08-3.48) p=<0.0001		4.60 (3.22-6.57) p=<0.0001 c=0.89 (0.82-0.97)	4.15 (2.87-5.99) p=<0.0001
Follow-up 16-20 years from onset (n=1172)									
<48	4 (40.0%)	2.04 (0.51-8.23)	2.89 (0.69-12.15)	0 (0.0%)	0.00 (0.00-infinity)	0.00 (0.00-infinity)	0 (0.0%)	1.92 (0.06-57.22)F	
48-52	15 (24.6%)	1.00	1.00	1 (1.6%)	1.00	1.00	1 (1.6%)	1.00	
53-57	52 (34.2%)	1.59 (0.81-3.12)	2.11 (1.02-4.37)	2 (1.3%)	0.80 (0.07-8.99)	1.16 (0.10-13.52)	0 (0.0%)	0.13 (0.01-3.34)F	
58-70	301 (51.3%)	3.23 (1.76-5.91)	3.50 (1.82-6.74)	21 (3.6%)	2.23 (0.29-16.84)	2.71 (0.34-21.38)	6 (1.0%)	0.45 (0.07-2.75)F	
>70	269 (74.3%)	8.87 (4.73-16.63) c=0.66	6.97 (3.48-13.94)	64 (17.7%)	12.89 (1.75-94.70) c=0.74	9.43 (1.21-73.56)	30 (8.3%)	3.70 (0.69-19.75)F c=0.77	
HbA1c AUC (OR per 10 units)		2.11 (1.83-2.43) p=<0.0001 c=0.69 (0.66-0.72)	1.78 (1.51-2.09) p=<0.0001		3.01 (2.45-3.71) p=<0.0001 c=0.81 (0.76-0.86)	2.45 (1.92-3.12) p=<0.0001		3.14 (2.40-4.12) p=<0.0001 c=0.86 (0.79-0.92)	2.87 (2.18-3.79) p=<0.0001

* Adjusted for age and sex
** Additionally adjusted for mean SBP, mean DBP, mean BMI, mean HDL, mean LDL, mean cholesterol, mean triglycerides, smoking.
F=Firth's penalized maximum likelihood estimation

Supplemental Table 2.2 Number and percent of albuminuria endpoints for each time period and the effect of HbA1c AUC categories on endpoints by using unadjusted and adjusted logistic regression.

	Microalbuminuria/Macroalbuminuria vs None			Macroalbuminuria vs None/Microalbuminria		
	n (%) events	Unadjusted	Adjusted**	n (%) events	Unadjusted	Adjusted*
Follow-up 8-9 years from onset (n=6476)						
<48	24 (3.6%)	1.06 (0.61-1.86)	1.02 (0.56-1.86)	7 (1.1%)	1.40 (0.47-4.18)	1.22 (0.41-3.67)
48-52	27 (3.4%)	1.00	1.00	6 (0.8%)	1.00	1.00
53-57	60 (5.4%)	1.62 (1.02-2.57)	1.70 (1.02-2.84)	8 (0.7%)	0.95 (0.33-2.75)	1.03 (0.36-2.99)
58-70	134 (5.5%)	1.65 (1.08-2.51)	1.55 (0.97-2.46)	29 (1.2%)	1.58 (0.65-3.81)	1.79 (0.74-4.35)
>70	145 (9.7%)	3.04 (2.00-4.63) c=0.60	2.52 (1.58-4.03)	21 (1.4%)	1.86 (0.75-4.64) c=0.56	1.97 (0.79-4.92)
HbA1c AUC (OR per 10 units)		1.39 (1.29-1.50) p=<0.0001 c=0.61 (0.58-0.64)	1.31 (1.20-1.43) p=<0.0001		1.21 (1.01-1.44) p=0.034 c=0.56 (0.49-0.63)	1.23 (1.04-1.46) p=0.017
Follow-up 10-11 years from onset (n=4490)						
<48	10 (3.6%)	1.09 (0.48-2.46)	1.09 (0.45-2.62)	2 (0.7%)	8.21 (0.39-172.33)F	
48-52	15 (3.3%)	1.00	1.00	0 (0.0%)	1.00	
53-57	39 (5.6%)	1.71 (0.93-3.15)	2.22 (1.14-4.35)	6 (0.9%)	8.45 (0.47-150.75)F	
58-70	84 (4.5%)	1.38 (0.79-2.41)	1.60 (0.85-3.01)	12 (0.6%)	6.11 (0.36-103.76)F	
>70	114 (9.5%)	3.07 (1.77-5.31) c=0.61	3.11 (1.65-5.84)	14 (1.2%)	11.09 (0.66-186.83)F c=0.61	
HbA1c AUC (OR per 10 units)		1.47 (1.34-1.62) p=<0.0001 c=0.62 (0.58-0.65)	1.42 (1.28-1.59) p=<0.0001		1.40 (1.09-1.80) p=0.0083 c=0.60 (0.50-0.69)	1.40 (1.10-1.78) p=0.0069
Follow-up 12-13 years from onset (n=2642)						
<48	1 (2.2%)	0.69 (0.08-6.07)	0.59 (0.07-5.23)	0 (0.0%)	3.46 (0.07-181.53)F	
48-52	5 (3.2%)	1.00	1.00	0 (0.0%)	1.00	
53-57	16 (4.4%)	1.40 (0.50-3.88)	1.52 (0.54-4.28)	2 (0.5%)	2.17 (0.10-45.80)F	
58-70	49 (3.9%)	1.22 (0.48-3.11)	0.91 (0.35-2.38)	8 (0.6%)	2.12 (0.12-37.20)F	
>70	93 (11.5%)	3.95 (1.58-9.89) c=0.65	2.51 (0.97-6.49)	10 (1.2%)	4.14 (0.24-71.49)F c=0.60	
HbA1c AUC (OR per 10 units)		1.87 (1.64-2.13) p=<0.0001 c=0.67 (0.63-0.72)	1.67 (1.42-1.97) p=<0.0001		2.07 (1.53-2.81) p=<0.0001 c=0.69 (0.56-0.82)	2.01 (1.46-2.77) p=<0.0001
Follow-up 14-15 years from onset (n=1959)						
<48	0 (0.0%)	0.00 (0.00-infinity)	0.00 (0.00-infinity)	0 (0.0%)	4.16 (0.08-228.66)F	
48-52	3 (3.4%)	1.00	1.00	0 (0.0%)	1.00	
53-57	6 (2.5%)	0.74 (0.18-3.03)	0.46 (0.10-2.11)	1 (0.4%)	1.13 (0.04-28.44)F	
58-70	40 (4.1%)	1.23 (0.37-4.05)	0.87 (0.26-2.93)	6 (0.6%)	1.20 (0.07-21.83)F	
>70	70 (11.0%)	3.54 (1.09-11.49) c=0.65	2.17 (0.64-7.31)	14 (2.2%)	4.16 (0.24-71.48)F, c=0.68	
HbA1c AUC (OR per 10 units)		1.94 (1.66-2.26) p=<0.0001 c=0.68 (0.63-0.74)	1.97 (1.61-2.41) p=<0.0001		2.52 (1.86-3.41) p=<0.0001 c=0.76 (0.65-0.88)	2.64 (1.88-3.72) p=<0.0001
Follow-up 16-20 years from onset (n=1262)						
<48	0 (0.0%)	0.00 (0.00-infinity)	0.00 (0.00-infinity)	0 (0.0%)	7.36 (0.12-455.21)F	
48-52	3 (4.8%)	1.00	1.00	0 (0.0%)	1.00	
53-57	9 (5.5%)	1.15 (0.30-4.39)	0.94 (0.23-3.79)	1 (0.6%)	1.15 (0.05-29.34)F	
58-70	21 (3.4%)	0.69 (0.20-2.37)	0.55 (0.15-1.95)	1 (0.2%)	0.30 (0.01-7.62)F	
>70	59 (14.5%)	3.34 (1.01-11.02) c=0.69	2.42 (0.70-8.32)	15 (3.7%)	4.95 (0.29-85.63)F c=0.79	
HbA1c AUC (OR per 10 units)		2.16 (1.80-2.59) p=<0.0001 c=0.70 (0.64-0.77)	2.14 (1.71-2.68) p=<0.0001		4.03 (2.74-5.92) p=<0.0001 c=0.88 (0.78-0.98)	3.83 (2.58-5.70) p=<0.0001

* Adjusted for age and sex
** Additionally adjusted for mean SBP, mean DBP, mean BMI, mean HDL, mean LDL, mean cholesterol, mean triglycerides, smoking.
F=Firth's penalized maximum likelihood estimation