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Cardiovascular and Kidney Outcomes Across the Glycemic Spectrum

Insights From the UK Biobank

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HEART iN DIABETES

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

Disclosures

- Grant support from the American Heart Association (940166, 979465)
- Consulting fees from CRISPR Therapeutics
  - Unrelated to this talk
- Advisory board of Miga Health
  - Unrelated to this talk

Dysglycemia is strongly linked to cardiovascular and kidney disease

- Type 2 diabetes (T2D) is a well-established risk factor for atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), and heart failure
  - Conditions commonly coexist in patients with T2D and contribute additively to poorer prognosis
  - Therapies that reduce cardiovascular/kidney risk in T2D (e.g., SGLT2i, GLP-1 RA) now considered the therapeutic standard irrespective of glycemic control[1]

[1]Kalyani RR. *New Engl J Med.* 2021

Dysglycemia is strongly linked to cardiovascular and kidney disease

- **Pre-diabetes** (hemoglobin A1c [HbA1c] ≥5.7% and <6.5%) is substantially more common than T2D
  - Affects 1 in 3 U.S. adults[1] and 1 in 5 U.S. adolescents[2]
  - Associated with subclinical alterations in cardiac structure and function[3]
  - May be associated with increased cardiovascular/kidney disease risk even in the absence of progression to frank T2D[4]
  - Current guidelines for pre-diabetes focus on glycemic control and prevention of progression to T2D

[1]Bullard KM et al. *Diabetes Care.* 2013; [2]Andes LJ et al. *JAMA Pediatrics.* 2020; [3]Selvin E et al. *Circulation.* 2014; [4]Cai X et al. *BMJ.* 2020

Dysglycemia is strongly linked to cardiovascular and kidney disease

- **Few data exist that comprehensively evaluate the risk of cardio-renal outcomes across the glycemic spectrum**, with a focus on HbA1c levels below the threshold for T2D

Are HbA1c levels associated with incident cardiovascular and kidney disease at levels below the threshold for diabetes?

Methods

Participants

- Individuals with HbA1c measured at baseline and without prevalent T1D, ASCVD, CKD, or heart failure

Exposures

- Primary: T2D (self-reported T2D, HbA1c ≥6.5% or use of insulin) vs. pre-diabetes (HbA1c ≥5.7% and <6.5%, no self-reported T2D) vs. normoglycemia
- Secondary: HbA1c as a continuous variable

Co-primary outcomes

- Incident ASCVD (composite of coronary artery disease, ischemic stroke, peripheral artery disease), CKD, and heart failure

Main statistical analysis: Cox proportional hazards models

- Adjusted for demographic, lifestyle, and cardiovascular risk factors

Results (N=336,709)

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Characteristic	Type 2 diabetes (n=12,717 [3.8%])	Pre-diabetes (n=46,911 [13.9%])	Normoglycemia (n=277,081 [82.3%])	P-value
Age, y	59.1 (7.2)	59.4 (7.0)	55.6 (8.1)	<0.001
Female sex	5,152 (40.5%)	26,452 (56.4%)	154,968 (55.9%)	<0.001
White	11,049 (86.9%)	42,564 (90.7%)	266,962 (96.3%)	<0.001
Townsend deprivation index (median [IQR])	-1.4 [-3.2, 1.8]	-2.0 [-3.6, 0.8]	-2.3 [-3.7, 0.1]	<0.001
Smoking status • Current • Former • Never	 1,427 (11.2%) 5,138 (40.4%) 6,152 (48.4%)	 6,891 (14.7%) 16,435 (35.0%) 23,585 (50.3%)	 25,931 (9.4%) 93,332 (33.7%) 157,818 (57.0%)	<0.001
Daily vegetable/fresh fruit portions	7 [5, 9]	7 [5, 9]	6 [5, 9]	<0.001
Body mass index, kg/m^2	31.6 (5.8)	28.9 (5.2)	26.8 (4.4)	<0.001
SBP, mmHg	144.9 (18.3)	143.7 (19.5)	138.8 (19.5)	<0.001
Antihypertensive medication use	6,803 (53.4%)	13,063 (27.8%)	40,471 (14.6%)	<0.001
Cholesterol-lowering medication use	7,944 (62.5%)	11,296 (24.1%)	27,042 (9.8%)	<0.001
Total cholesterol, mg/dL	186.1 (46.4)	225.0 (46.3)	224.1 (41.5)	<0.001
HDL cholesterol, mg/dL	46.5 (12.1)	53.8 (14.0)	57.5 (14.7)	<0.001
C-reactive protein (median [IQR]), mg/L	2.1 [1.0, 4.4]	1.9 [1.0, 3.9]	1.2 [0.6, 2.5]	<0.001
Urine microalbumin/creatinine ≥30 mg/g	1,761 (13.8%)	2,548 (5.4%)	9,459 (3.4%)	<0.001

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Incident outcomes by baseline glycemic status

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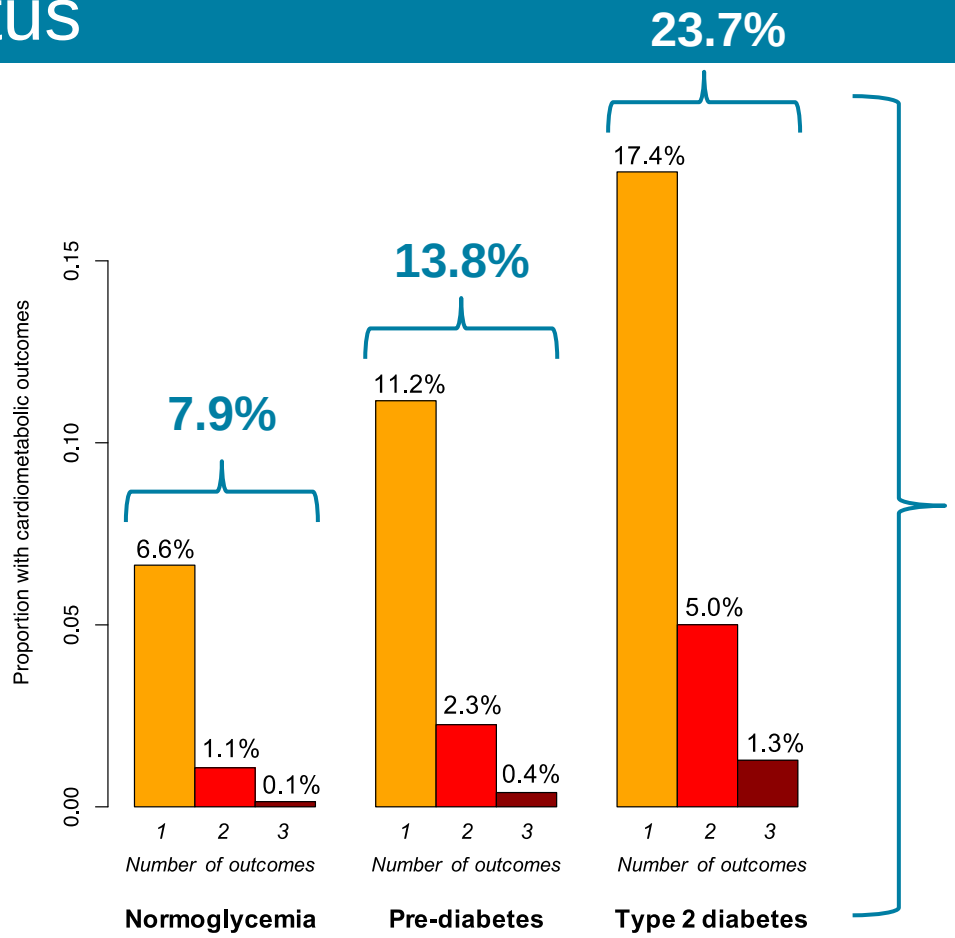

*Cumulative incidence of ASCVD, CKD, and/or heart failure over median (IQR) follow-up of **11.1 (10.4-11.7) years***

Cumulative incidence and incidence rates of co-primary outcomes

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		Atherosclerotic cardiovascular disease		Chronic kidney disease		Heart failure	
	No. at risk	Cum. incidence	IR per 1,000 person-years (95% CI)	Cum. incidence	IR per 1,000 person-years (95% CI)	Cum. Incidence	IR per 1,000 person-years (95% CI)
Normoglycemia	277,081	5.7%	5.28 (5.20-5.36)	2.0%	1.79 (1.74-1.83)	1.5%	1.37 (1.33-1.41)
Pre-diabetes	46,911	10.0%	9.44 (9.17-9.71)	4.0%	3.64 (3.47-3.80)	2.9%	2.63 (2.49-2.77)
Type 2 diabetes	12,717	16.8%	16.51 (15.81-17.21)	9.3%	8.66 (8.17-9.16)	5.2%	4.77 (4.41-5.14)

Cumulative incidence and incidence rates of co-primary outcomes

		Atherosclerotic cardiovascular disease		Chronic kidney disease		Heart failure	
	No. at risk	Cum. incidence	IR per 1,000 person-years (95% CI)	Cum. incidence	IR per 1,000 person-years (95% CI)	Cum. incidence	IR per 1,000 person-years (95% CI)
Normoglycemia	277,081	5.7%	5.28 (5.20-5.36)	2.0%	1.79 (1.74-1.83)	1.5%	1.37 (1.33-1.41)
Pre-diabetes	46,911	10.0%	9.44 (9.17-9.71)	4.0%	3.64 (3.47-3.80)	2.9%	2.63 (2.49-2.77)
Pre-diabetes without progression to type 2 diabetes before event	46,109	9.0%	8.49 (8.23-8.75)	3.4%	3.13 (2.97-3.28)	2.5%	2.30 (2.16-2.43)
Type 2 diabetes	12,717	16.8%	16.51 (15.81-17.21)	9.3%	8.66 (8.17-9.16)	5.2%	4.77 (4.41-5.14)

Progression of pre-diabetes and incident events

- Of 46,911 with pre-diabetes at baseline, 6,589 (14.0%) developed incident T2D during follow-up

- Among 6,476 individuals with pre-diabetes who developed ≥1 outcome:
  - 1,930 (29.8%) progressed to T2D during follow-up
  - 802 (12.4%) developed T2D prior to a cardiovascular/kidney diagnosis

Multivariable-adjusted hazard ratios for co-primary outcomes

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	Atherosclerotic cardiovascular disease		Chronic kidney disease		Heart failure	
	Model 1	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
	Hazard ratio (95% CI)	***Hazard ratio (95% CI)***	***Hazard ratio (95% CI)***	***Hazard ratio (95% CI)***	***Hazard ratio (95% CI)***	***Hazard ratio (95% CI)***
Normoglycemia	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Pre-diabetes	1.44 (1.39-1.49)**	1.11 (1.08-1.15)**	1.48 (1.40-1.56)**	1.08 (1.02-1.14)*	1.46 (1.38-1.56)**	1.07 (1.01-1.14)^
Type 2 diabetes	2.25 (2.15-2.36)**	1.44 (1.37-1.51)**	3.60 (3.37-3.84)**	1.57 (1.46-1.69)**	2.48 (2.28-2.69)**	1.25 (1.14-1.37)**

^P<0.05; *P<0.017; **P<0.001
Model 1: Adjusted for age, age^2, sex, and race
Model 2: Adjusted for age, age^2, sex, race, Townsend deprivation index, smoking status, alcohol consumption, vegetable and fresh fruit intake, history of cancer, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, body mass index, C-reactive protein, urinary albumin-to-creatinine ratio

Multivariable-adjusted hazard ratios for secondary outcomes

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	Coronary artery disease		Ischemic stroke		Peripheral artery disease		All-cause mortality	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	HR (95% CI)	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*	*HR (95% CI)*
Normo-glycemia	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Pre-diabetes	1.42 (1.37-1.47)	1.10 (1.06-1.14)	1.28 (1.15-1.42)	1.06 (0.95-1.18)	1.80 (1.64-1.97)	1.27 (1.15-1.39)	1.31 (1.26-1.37)	1.10 (1.05-1.14)
Type 2 diabetes	2.23 (2.12-2.34)	1.40 (1.33-1.48)	1.96 (1.70-2.27)	1.47 (1.25-1.72)	3.23 (2.87-3.63)	1.90 (1.67-2.16)	1.84 (1.74-1.95)	1.38 (1.30-1.47)

Model 1: Adjusted for age, age^2, sex, and race
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Population attributable risk proportion for pre-diabetes vs. T2D

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	Atherosclerotic cardiovascular disease	Chronic kidney disease	Heart failure
Pre-diabetes	8.1%	9.8%	9.9%
Type 2 diabetes	5.9%	10.5%	7.1%

At what HbA1c level do risks nadir?

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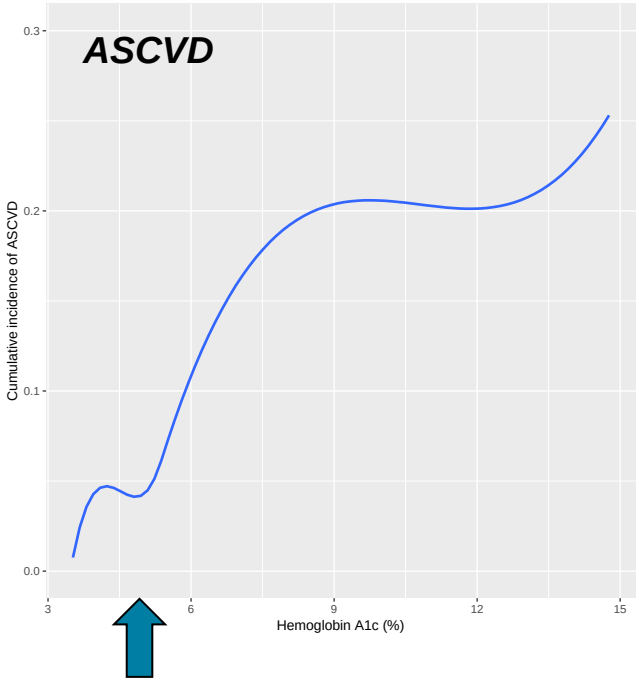

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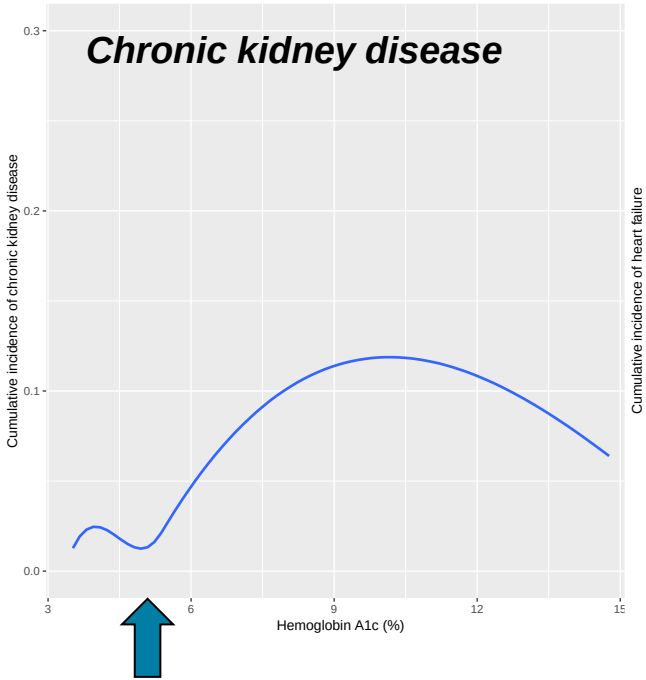

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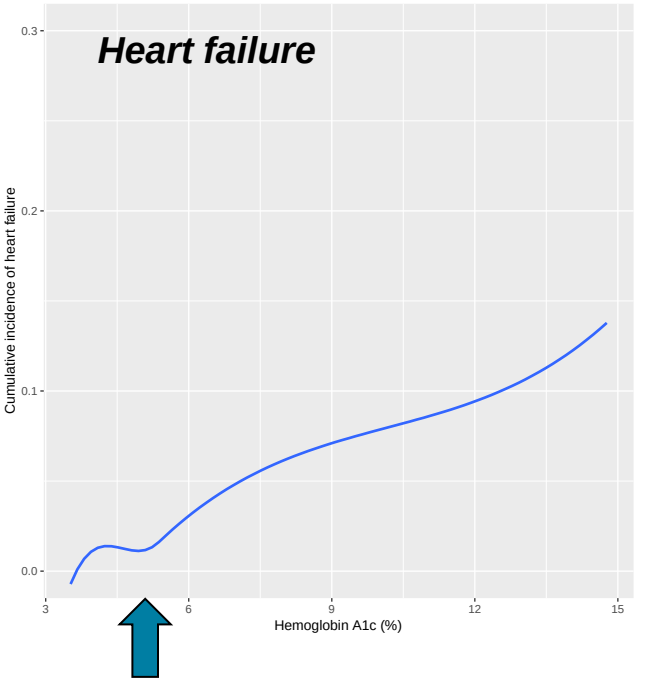

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Substantial gradient of risk across HbA1c levels below the threshold for diabetes

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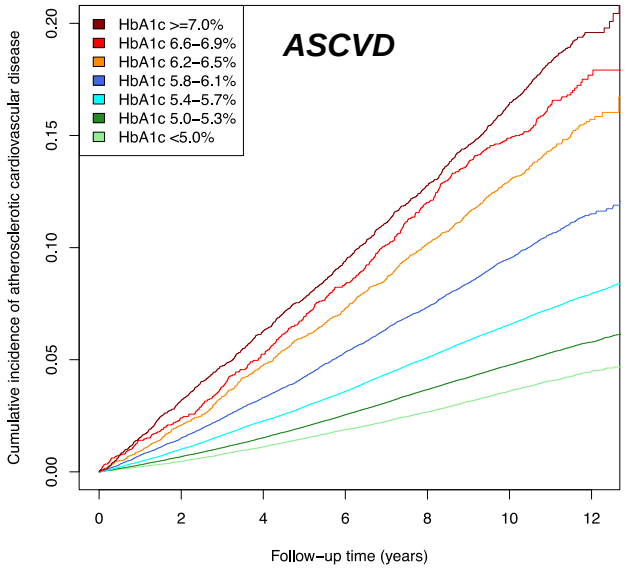

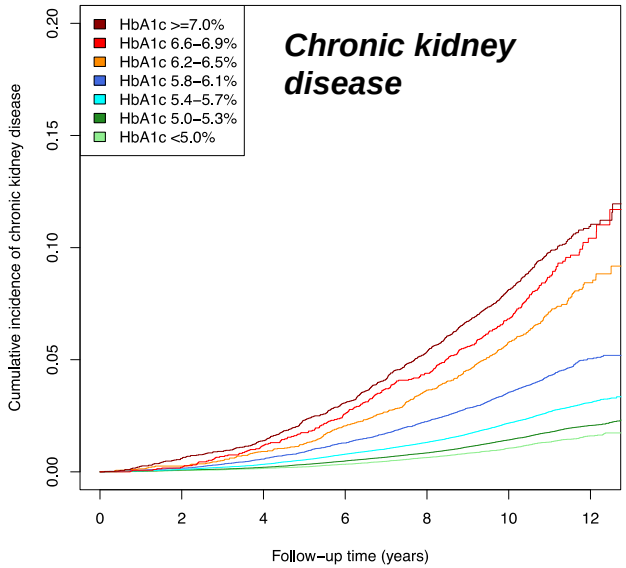

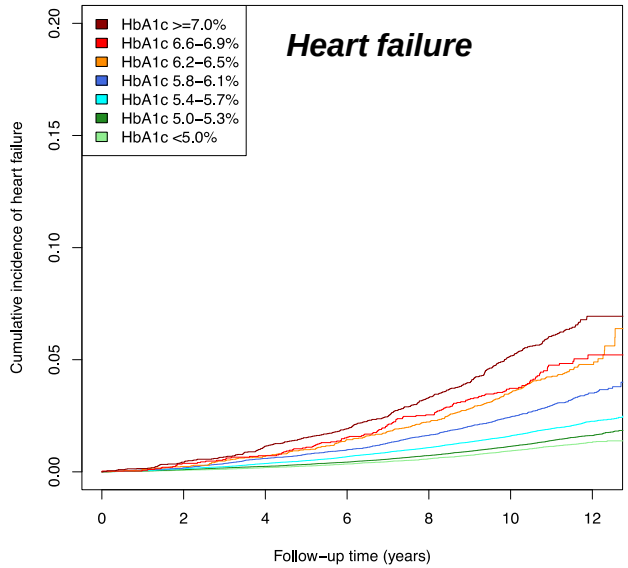

Adjusted risk across levels of HbA1c

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	Atherosclerotic cardiovascular disease	Chronic kidney disease	Heart failure
HbA1c	***Hazard ratio (95% CI)***	***Hazard ratio (95% CI)***	***Hazard ratio (95% CI)***
<5.0%	1.00 (ref)	1.00 (ref)	1.00 (ref)
5.0-5.3%	1.03 (0.98-1.08)	0.96 (0.88-1.05)	0.95 (0.87-1.05)
5.4-5.7%	1.08 (1.03-1.14)*	1.00 (0.91-1.09)	0.95 (0.86-1.05)
5.8-6.1%	1.19 (1.12-1.27)**	1.07 (0.97-1.18)	1.00 (0.89-1.12)
6.2-6.5%	1.29 (1.19-1.41)**	1.26 (1.10-1.43)**	1.04 (0.89-1.21)
6.6-6.9%	1.40 (1.26-1.55)**	1.35 (1.16-1.57)**	0.98 (0.81-1.20)
≥7.0%	1.51 (1.39-1.64)**	1.44 (1.27-1.63)**	1.30 (1.12-1.50)**

^P<0.05; *P<0.017; **P<0.001

Models adjusted for age, age^2, sex, race, Townsend deprivation index, smoking status, alcohol consumption, vegetable and fresh fruit intake, history of cancer, systolic blood pressure, antihypertensive medication use, non-HDL cholesterol, cholesterol-lowering medication use, body mass index, C-reactive protein, urinary albumin-to-creatinine ratio

Accumulation of multimorbidity by glycemia status

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Glycemic status	First outcome	No. (%)	Time to first diagnosis, years, median [IQR]	Second outcome, no. (% with first outcome)	Time to second diagnosis, median [IQR]
Normoglycemia (n=277,081)	ASCVD	15,119 (5.5%)	6.1 [3.4, 8.5]	2,361 (15.6%)	0.1 [0, 2.8]
	CKD	4,396 (1.6%)	8.1 [5.6, 9.8]	514 (11.7%)	0.9 [0.1, 2.8]
	Heart failure	2,254 (0.8%)	7.5 [4.7, 9.5]	498 (22.1%)	1.0 [0.2, 2.8]
Pre-diabetes (n=46,911)	ASCVD	4,396 (9.4%)	5.8 [3.1, 8.4]	856 (19.5%)	0.5 [0, 3.4]
	CKD	1,416 (3.0%)	7.8 [5.3, 9.6]	211 (14.9%)	1.3 [0.3, 3.3]
	Heart failure	664 (1.4%)	7.2 [4.3, 9.4]	176 (26.5%)	1.0 [0.3, 3.0]
Type 2 diabetes (n=12,717)	ASCVD	1,937 (15.2%)	5.6 [2.9, 8.3]	501 (25.6%)	0.7 [0, 3.4]
	CKD	840 (6.6%)	7.2 [5.0, 9.4]	183 (21.8%)	0.9 [0.1, 2.6]
	Heart failure	240 (1.9%)	6.9 [4.0, 9.2]	115 (47.9%)	0.7 [0.1, 1.9]

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	Heart failure	2,254 (0.8%)	7.5 [4.7, 9.5]	498 (22.1%)	1.0 [0.2, 2.8]
Pre-diabetes (n=46,911)	ASCVD	4,396 (9.4%)	5.8 [3.1, 8.4]	856 (19.5%)	0.5 [0, 3.4]
	CKD	1,416 (3.0%)	7.8 [5.3, 9.6]	211 (14.9%)	1.3 [0.3, 3.3]
	Heart failure	664 (1.4%)	7.2 [4.3, 9.4]	176 (26.5%)	1.0 [0.3, 3.0]
Type 2 diabetes (n=12,717)	ASCVD	1,937 (15.2%)	5.6 [2.9, 8.3]	501 (25.6%)	0.7 [0, 3.4]
	CKD	840 (6.6%)	7.2 [5.0, 9.4]	183 (21.8%)	0.9 [0.1, 2.6]
	Heart failure	240 (1.9%)	6.9 [4.0, 9.2]	115 (47.9%)	0.7 [0.1, 1.9]

Predictors of elevated risk among individuals without T2D

- Interaction analyses revealed significant interactions with glycemic status for ≥2 outcomes:
  - Smoking status
  - Medication-adjusted SBP
  - Medication-adjusted non-HDL cholesterol
  - C-reactive protein
- Based on these results, we defined “high-risk pre-diabetes” as individuals with pre-diabetes who were current or former smokers or who had SBP, non-HDL cholesterol, and C-reactive protein each in the top tertile of the study sample

“High-risk” pre-diabetes represents similar risk vs. T2D

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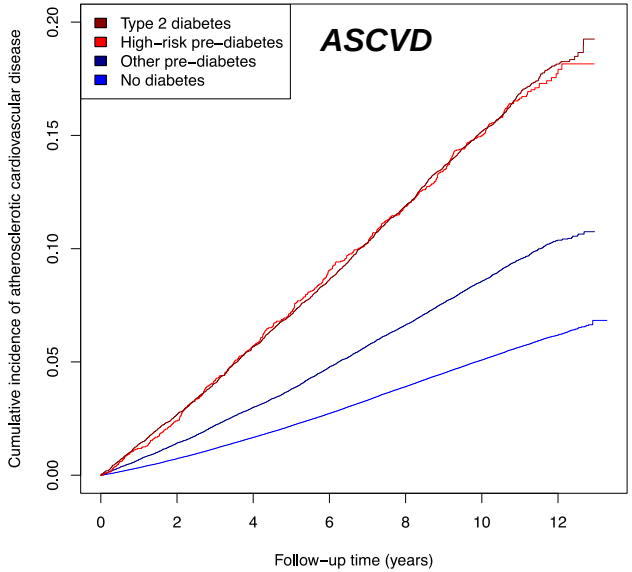

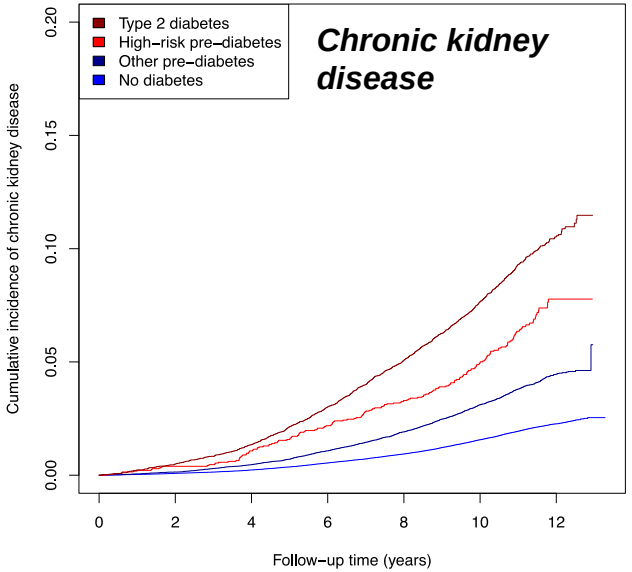

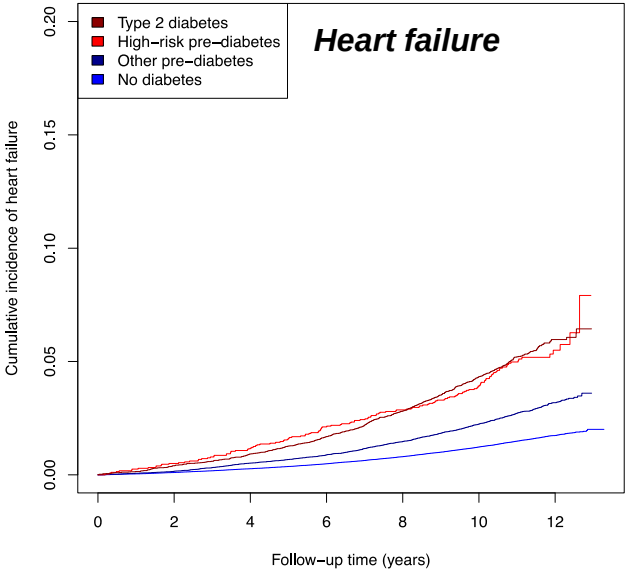

Summary of findings

- In a large population-based cohort without established CV or kidney disease, a substantial risk gradient was evident across HbA1c levels in the pre-diabetic range and below
- Population attributable risks for baseline glycemic status were greater for pre-diabetes vs. T2D for incident ASCVD and heart failure
- >2/3 of pre-diabetic individuals who developed CV or kidney disease did not progress to frank T2D over a median 11 years of follow-up
- Individuals with “high-risk pre-diabetes” had similar absolute risks vs. those with T2D

Implications

- HbA1c may be better considered as a continuous measure of risk, rather than dichotomized as ≥6.5% vs. <6.5%

HbA1c and subclinical atherosclerosis

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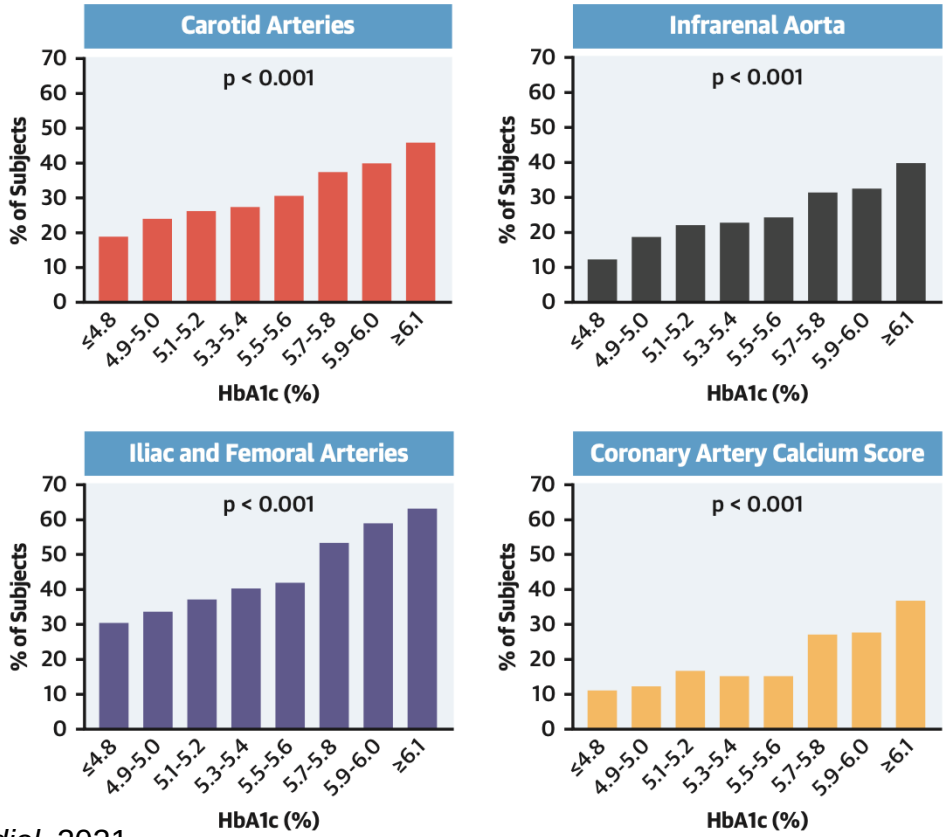

Rossello X, et al. *J Am Coll Cardiol.* 2021

Implications

- HbA1c may be better considered as a continuous measure of risk, rather than dichotomized as ≥6.5% vs. <6.5%
- Pre-diabetes signals heightened risk even without progression to T2D
  - May represent a relevant entity among middle-aged individuals
- Cardiovascular and kidney outcomes trials may be feasible in high-risk subsets of pre-diabetic individuals
- Findings highlight the need to design specific cardiovascular and kidney risk-reducing strategies across the glycemic spectrum

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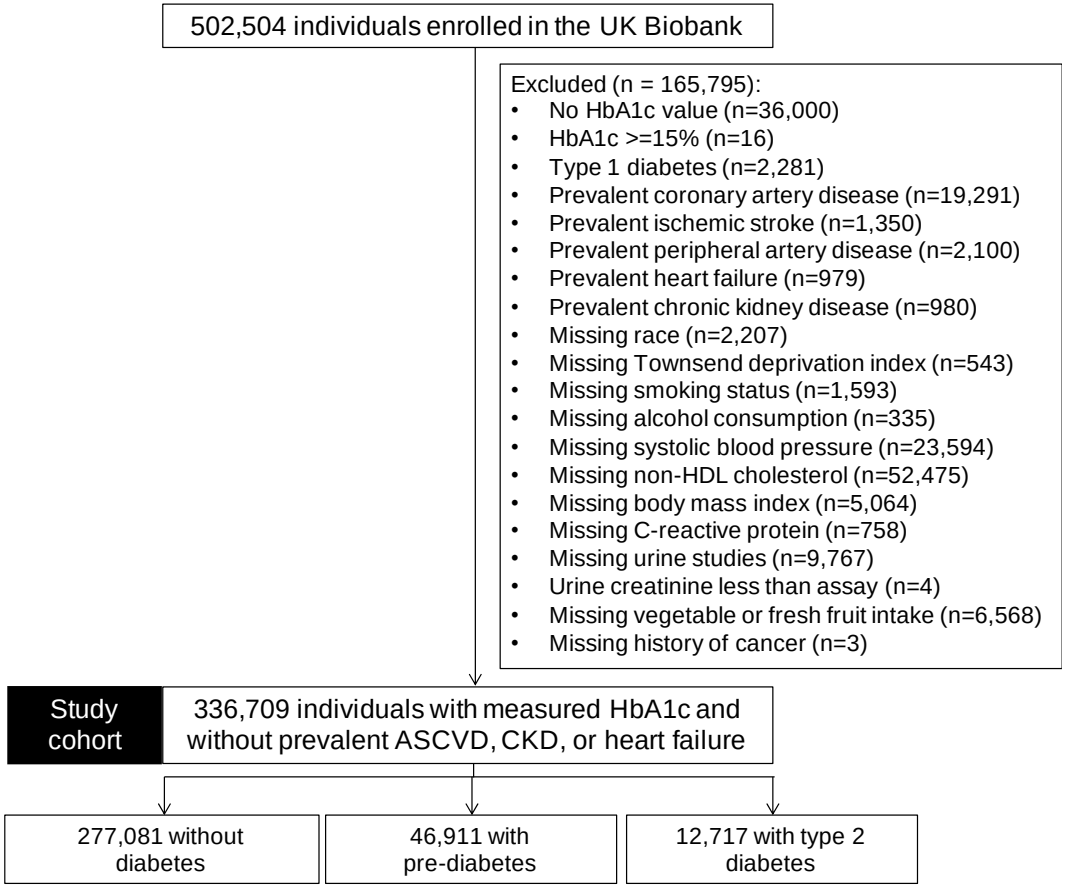
Supplemental Slides

Study cohort



Population attributable risk proportion for pre-diabetes vs. T2D

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Full study cohort:

	Atherosclerotic cardiovascular disease	Chronic kidney disease	Heart failure
Pre-diabetes	8.1%	9.8%	9.9%
Type 2 diabetes	5.9%	10.5%	7.1%

Excluding individuals without T2D at baseline who developed incident T2D prior to a study endpoint:

	Atherosclerotic cardiovascular disease	Chronic kidney disease	Heart failure
Pre-diabetes	6.0%	6.7%	6.8%
Type 2 diabetes	6.2%	11.2%	7.6%

Strengths and limitations

- Strengths
  - Uniquely large cohort with comprehensive, uniform phenotyping and median follow-up duration of 11 years
- Limitations
  - Healthy participant bias in UK Biobank
  - Limited power to test relationships in non-White subgroups
  - Parameters used to define “high-risk pre-diabetes” were determined *post hoc* and require external validation