

Borderline HbA1c Levels Among Nondiabetic Patients Associated with Increased Cardiovascular Disease Risk

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Key Findings:

- Nondiabetic patients with higher HbA1c levels are more likely to experience novel myocardial infarction (MI). Those with an average HbA1c of 5.4–5.6% are 6% more likely compared to those with an HbA1c between 5.0 and 5.3%. The increase is greater with higher average HbA1c levels, reaching 21% more likely among those with an HbA1c of 6.1–6.4%.
- Nondiabetic patients with lower HbA1c levels are generally less likely to have a novel stroke, though the likelihood increases at the lowest HbA1c levels. Those with an HbA1c of 6.1–6.4% are 9% more likely, and those with an HbA1c of 4.0–4.9% are 6% more likely compared to those with an HbA1c between 5.0 and 5.3%.

While HbA1c is a central metric for managing diabetes, its role in cardiovascular risk among nondiabetic individuals remains less understood. Clinical attention often focuses on thresholds for diagnosing diabetes (HbA1c \geq 6.5%), but growing evidence suggests that glycemic variation below this threshold may also influence cardiovascular outcomes, especially for HbA1c values considered borderline, or pre-diabetic (HbA1c between 5.7 and 6.4%).^{1,2}

To understand the relationship between HbA1c levels and cardiovascular events for nondiabetic patients, we studied 3,344,135 patients without type 2 diabetes with multiple HbA1c readings. HbA1c levels were averaged over a three-year observation window, beginning at least one year after a patient's first clinical encounter. We accounted for patient demographics, smoking status, BMI classification, social vulnerability, and comorbidities in our analysis.

First, we evaluated the likelihood of experiencing an initial MI by patients' average HbA1c level. We found that, as average HbA1c went up, patients were more likely to experience an initial MI, as seen in Figure 1. Individuals with an average HbA1c between 5.4 and 5.6% were 6% more likely to experience an MI, those with an HbA1c between 5.7 and 6.0% were 12% more likely, and those with an HbA1c between 6.1 and 6.4% were 21% more likely compared to patients with an HbA1c between 5.0 and 5.3%.

Likelihood of Novel MI by Average HbA1c

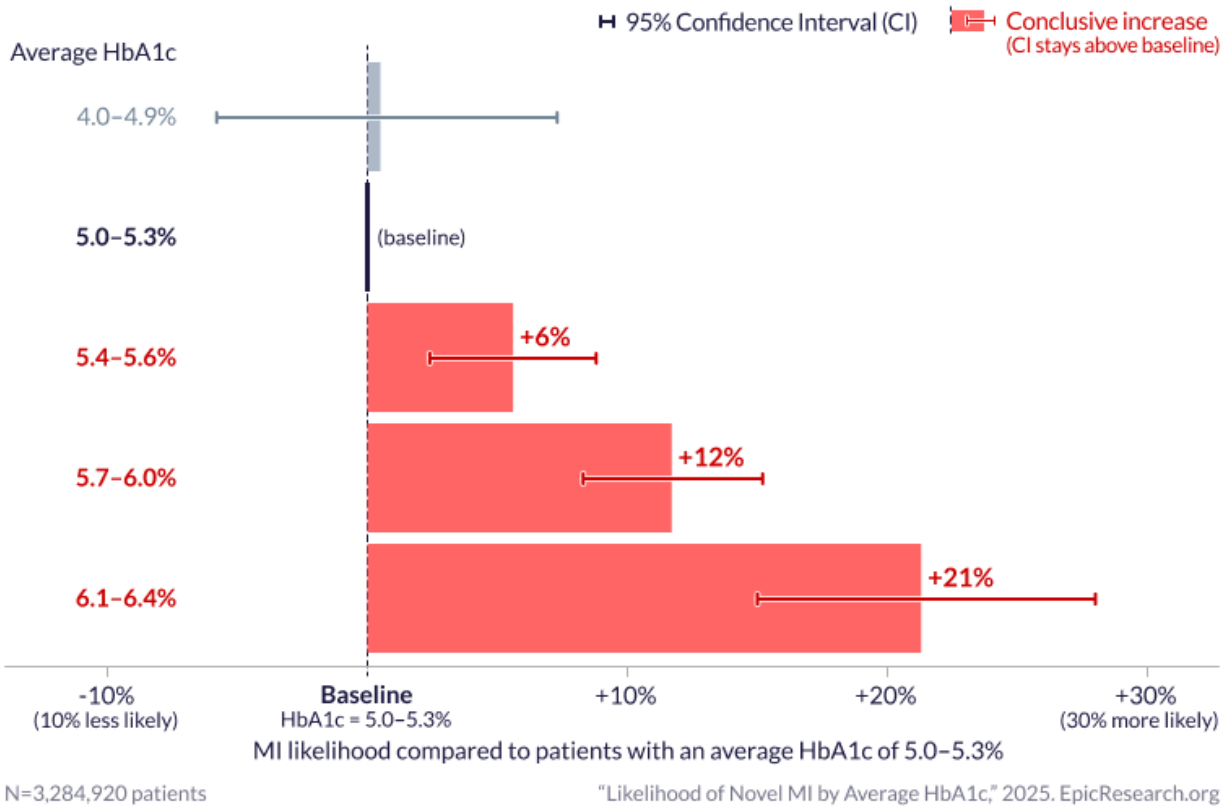


Figure 1. The likelihood of a nondiabetic patient experiencing a novel MI by their average HbA1c level.

We evaluated the likelihood of experiencing a novel stroke by patients' average HbA1c level. We found that the likelihood of stroke was lowest among patients with an average HbA1c of 5.0-5.3%, and the likelihood was greater for those with a higher or lower average HbA1c. Patients were 3% more likely to have a stroke when their average HbA1c was between 5.7 and 6.0% compared to those with an HbA1c between 5.0 and 5.3%, as seen in Figure 2. That likelihood was even higher among patients with an HbA1c between 4.0 and 4.9% (6% more likely) and an HbA1c between 6.1 and 6.4% (9% more likely).

Likelihood of Novel Stroke by Average HbA1c

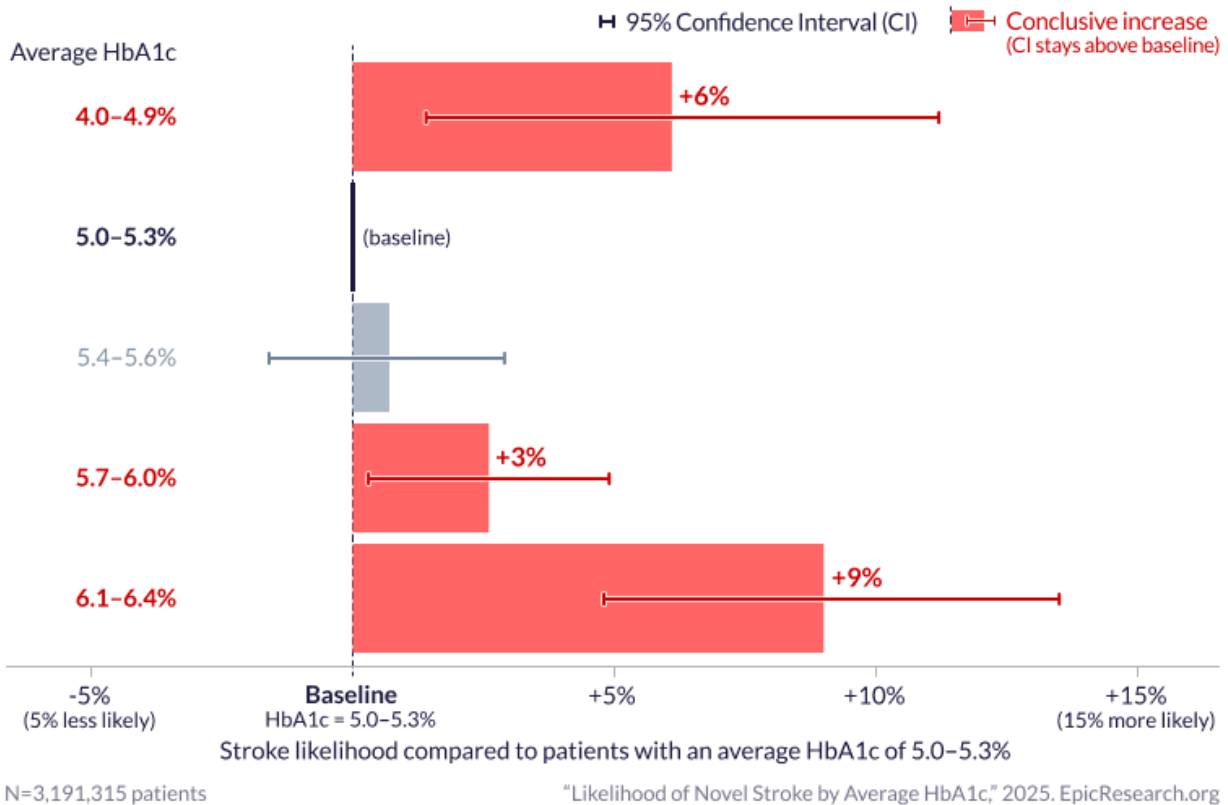


Figure 2. The likelihood of a nondiabetic patient experiencing a novel stroke by their average HbA1c level.

These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 300 million patient records from 1,700 hospitals and more than 40,000 clinics from all 50 U.S. states, Lebanon, and Saudi Arabia. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.

References

- Butalia S, Chu LM, Dover DC, et al. Association Between Hemoglobin A1c and Development of Cardiovascular Disease in Canadian Men and Women Without Diabetes at Baseline: A Population-Based Study of 608 474 Adults. *J Am Heart Assoc.* 2024;13(9):e031095. doi:10.1161/JAHA.123.031095
- Sinning C, Makarova N, Völzke H, et al. Association of glycosylated hemoglobin A1c levels with cardiovascular outcomes in the general population: results from the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) consortium. *Cardiovasc Diabetol.* 2021;20(1):223. Published 2021 Nov 15. doi:10.1186/s12933-021-01413-4

Data Definitions

Term	Definition
Study period	1/1/2000 – 4/28/2025
Study population: inclusions	Patients with at least two HbA1c results in the three years after the index date

	Index date: The date of their first HbA1c value at least a year after their first face-to-face encounter
Study population: exclusions	<p>Patients with:</p> <ul style="list-style-type: none"> • HbA1c value of 6.5% or higher within three years of their index date • No second HbA1c result in the three years after the index date • A documented pregnancy between the index date and the following three years • A history of the outcome for each analysis • Documentation of any of the following: <ul style="list-style-type: none"> • Type 1 diabetes: ICD-10-CM code E10* • Type 2 diabetes: ICD-10-CM code E11* • Other diabetes: ICD-10-CM code E08*-E09*, E13* • Hemolytic anemia: ICD-10-CM code D55*-D59* • Aplastic anemia: ICD-10-CM code D60*-D64* • Methemoglobinemia: ICD-10-CM code D74* • Other/Unspecified disease of blood/blood forming organs: ICD-10-CM code D75* • Cancer: ICD-10-CM code C* • HIV: ICD-10-CM code B20*
Exposure	Time-weighted average HbA1c over the three years starting at the index date
Outcomes	A diagnosis of stroke or MI
Confounders	<p>Age at index (30-49, 50-64, 65+)</p> <p>BMI classification:</p> <ul style="list-style-type: none"> • Underweight: <18.5 • Healthy: 18.5-<25 • Overweight: 25-<30 • Obese: 30+ <p>Weighted average HbA1c:</p> <ul style="list-style-type: none"> • 4.0-4.9% • 5.0-5.3% • 5.4-5.6% • 5.7-6.0% • 6.1-6.4% <p>CVD prior to or within three years of index date</p> <p>Family history of CVD</p> <p>Gestational diabetes prior to or within three years of index date</p> <p>Hyperlipidemia prior to or within three years of index date</p> <p>Hypertension prior to or within three years of index date</p> <p>Race and ethnicity: Hispanic, Asian Non-Hispanic, Black Non-Hispanic, Other Non-Hispanic, White Non-Hispanic)</p> <p>RUCA: Metropolitan, Micropolitan, Small Town, Rural</p> <p>Legal sex</p> <p>Documentation of current or past smoking</p> <p>Social Vulnerability Index quintile</p>
Race and ethnicity	Mutually exclusive categories for Hispanic, Asian Non-Hispanic, Black Non-Hispanic, Other Non-Hispanic, and White Non-Hispanic.
Model specifications	Cox PH Regressions

Stratifications	Age at index: 35-49, 50-64, 65+
Stroke	A diagnosis with ICD-10-CM code I60*, I63*, I69.3*, Z86.73, or G45.9
MI	A diagnosis with ICD-10-CM code I21*, I22*, or I23*
CVD	Diagnosis with ICD-10-CM code I20*-I26*, I30*-I49*, I51*, I70*-I79*
Family history of CVD	Diagnosis with ICD-10-CM code Z82.4*
Gestational diabetes	Diagnosis of O24.1* or O24.4*
HbA1c	Lab result with LOINC code 17856-6, 17855-8, 4548-4, or 4549-2 with a result value between 4.0% and 6.4%
Hyperlipidemia	Diagnosis of ICD-10-CM E78.2*-E78.5*
Hypertension	Diagnosis of ICD-10-CM I10*-I16*
Face-to-face encounter	An encounter with a type of Emergency, Office Visit, Well Child, Follow-up, Telemedicine, Urgent Care, Walk-In, Routine Prenatal, Postpartum Visit, or Fetal Care Consult

Likelihood of Novel MI by Average HbA1c

	Odds Ratio	Lower CI	Upper CI
Smoking History	1.459	1.428	1.491
Family History of CVD	2.127	2.078	2.176
Hyperlipidemia	1.086	1.059	1.114
Hypertension	1.522	1.482	1.563
Asian	0.715	0.660	0.773
Black	1.088	1.048	1.129
Hispanic	0.847	0.805	0.891
Other Race	0.905	0.870	0.943
RUCA Micropolitan	1.219	1.169	1.272
RUCA Rural	1.350	1.268	1.437
RUCA Small Town	1.233	1.162	1.308
Female Sex	0.648	0.634	0.663
SVI Quintile 2	0.999	0.965	1.034
SVI Quintile 3	1.091	1.053	1.131
SVI Quintile 4	1.060	1.023	1.099
SVI Quintile 5	1.134	1.093	1.176
BMI Category Overweight	0.955	0.924	0.987
BMI Category Underweight	1.693	1.491	1.923
BMI Category Obese	1.037	1.004	1.071
HbA1c 4.0 to 4.9	1.005	0.942	1.073
HbA1c 5.4 to 5.6	1.056	1.024	1.088
HbA1c 5.7 to 6.0	1.117	1.083	1.152
HbA1c 6.1 to 6.4	1.213	1.150	1.280

Age 50-64	1.505	1.458	1.552
Age 65-79	2.255	2.177	2.336
Age 80+	5.715	5.433	6.011
CVD	1.939	1.894	1.984
Gestational Diabetes	0.639	0.458	0.890

Likelihood of Novel Stroke by Average HbA1c

	Odds Ratio	Lower CI	Upper CI
Smoking History	1.261	1.241	1.281
Family History of CVD	1.577	1.549	1.607
Hyperlipidemia	1.009	0.991	1.027
Hypertension	1.354	1.329	1.380
Asian	0.828	0.786	0.873
Black	1.179	1.148	1.211
Hispanic	1.011	0.977	1.046
Other Race	1.049	1.020	1.078
RUCA Micropolitan	1.106	1.070	1.142
RUCA Rural	1.046	0.993	1.103
RUCA Small Town	1.055	1.007	1.106
Female Sex	0.968	0.952	0.984
SVI Quintile 2	1.034	1.008	1.061
SVI Quintile 3	1.092	1.063	1.122
SVI Quintile 4	1.152	1.122	1.183
SVI Quintile 5	1.226	1.193	1.259
BMI Category Overweight	0.972	0.950	0.995
BMI Category Underweight	1.296	1.177	1.426
BMI Category Obese	0.952	0.931	0.974
HbA1c 4.0 to 4.9	1.061	1.014	1.112
HbA1c 5.4 to 5.6	1.007	0.984	1.029
HbA1c 5.7 to 6.0	1.026	1.003	1.049
HbA1c 6.1 to 6.4	1.090	1.048	1.135
Age 50-64	1.690	1.651	1.731
Age 65-79	3.345	3.258	3.434
Age 80+	8.032	7.733	8.343
CVD	1.541	1.515	1.568
Gestational Diabetes	0.824	0.679	0.999