

How Should we Interpret Racial Differences in Hemoglobin A1C (HbA1C)?

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Hemoglobin A1C – Fundamental to Diabetes Care

- Standard measure used to monitor glycemic control in persons with diabetes
 - Used to monitor and guide treatment
- Screening and diagnostic test for prediabetes and diabetes
- Surrogate endpoint for clinical trials of glucose-lowering therapies in type 1 and type 2 diabetes trials (FDA criteria)



Advantages of HbA1c for Diabetes Diagnosis and Care

- Less biologic variability (vs fasting or 2-hr glucose)
- Index of overall glycemic exposure
- Well-standardized assay methods
- Eliminates the need for fasting or timed samples
- Relatively unaffected by acute factors (activity, diet, acute illness)
- Familiar to patients and providers
- Associated with major complications of diabetes, with stronger associations than fasting glucose



Limitations of HbA1c?

1) Assay interferences

- Some Hb traits interfere with interpretation of HbA1c assays, but this is not true for the majority of Hb variants: www.ngsp.org

2) Some conditions interfere with HbA1c test results

- Altered red cell turnover, e.g. hemolytic anemia, transfusions, pregnancy, major blood loss

➤ Slightly higher levels of HbA1c in African Americans

- This has been cited repeatedly as a “limitation” of the HbA1c test
- This is NOT a limitation of the HbA1c assay



“...the use of HbA1c levels for diagnosing diabetes mellitus or prediabetes [in African Americans] is ill-advised.”

Nature Reviews Endocrinology 6, 589-593; October 2010

“Plasma glucose level is more valid than hemoglobin A1c for diagnosing prediabetes or diabetes in black persons.” Endocr Pract. 2012; 18:356-362

“A1c may not be valid for assessing and comparing glycemic control across racial and ethnic groups or as an indicator of health care disparities.” Diab Care 2007; 30(10):2453-2457

“In African descent populations in the United States, the utility of HbA1c is limited in screening for glycemic status, determining care methods, assessing risk of type 2 diabetes complications, or analyzing health disparities.” Prev Chronic Dis 2021;18:200365



“Racial Differences” in HbA1c in Adults without Diabetes

Mean HbA1c (%-points) in Adults without Diabetes According to Race/Ethnic Group, Popn-Based Cohorts

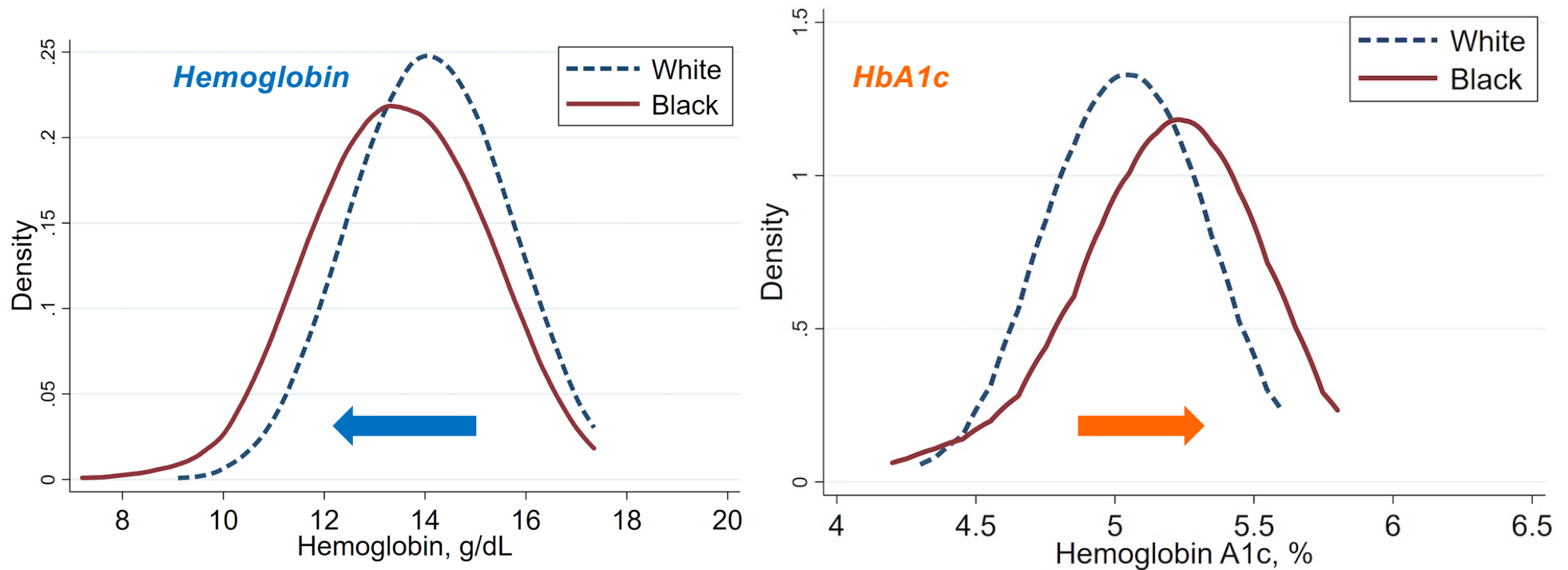
Black	White	Hispanic	Study Pop'n
-	5.4	5.5	HCHS/SOL (Hispanic) NHANES 2007-2012 (White)
5.6	5.3	-	CARDIA
5.4	5.3	5.3	NHANES 1999-2014
5.9	5.6	-	ARIC

References: Avilés-Santa et al, 2016; Carson et al, 2016; Selvin et al, 2014



Distributions of *hemoglobin* and *HbA1c* in young, healthy adults (NHANES)

Difference in HbA1c between Black and White Adults: ~0.2 %-points



Strong link between A1C and clinical outcomes

- Large and robust literature linking HbA1C with clinical outcomes
 - No evidence for racial differences in associations with outcomes or in clinical trials of glucose-lowering interventions (e.g. subgroup analysis in ACCORD)
- Most studies show higher risk of diabetes (e.g. DPP Trial) and its **complications** in Black adults and other racial or ethnic minority groups compared to White adults
- No racial differences in the correlations of HbA1c with average glucose (via CGM) or with fasting glucose

-Bergenstal et al 2018, Ann Int Med



No Evidence for Racial Differences in the Association of HbA1C with Complications of Diabetes

Annals of Internal Medicine

ORIGINAL RESEARCH

Racial Differences in Glycemic Markers: A Cross-sectional Analysis of Community-Based Data

Elizabeth Selvin, PhD, MPH; Michael W. Steffes, MD, PhD; Christie M. Ballantyne, MD; Ron C. Hoogeveen, PhD; Josef Coresh, MD, PhD; and Frederick L. Brancati, MD, MHS

No Racial Differences in the Association of Glycated Hemoglobin With Kidney Disease and Cardiovascular Outcomes

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Are There Clinical Implications of Racial Differences in HbA_{1c}?
A Difference, to Be a Difference, Must Make a Difference

Elizabeth Selvin

Diabetes Care 2016;39:1462–1467 | DOI: 10.2337/dc16-0042

For a difference, to be a difference, must make a difference.

- Gertrude Stein (attributed to...)



Why are there small but systematic differences in HbA1C by race?

- Glucose-independent race differences in HbA1C are **small**
 - ~0.2 %-points in HbA1c
 - In diabetes, any non-glycemic determinants will typically be dwarfed by differences in true hyperglycemia
- Small differences in HbA1C between groups (e.g. blacks vs whites) may be explained by “hematologic differences” in a **subgroup**
 - Emerging data suggest genetic differences in a **subgroup** may underlie small differences in HbA1c that are independent of glycemia



Analyses of biomarker traits in diverse UK biobank participants identify associations missed by European-centric analysis strategies

Quan Sun¹, Misa Graff², Bryce Rowland¹, Jia Wen³, Le Huang³, Tyne W. Miller-Fleming⁴, Jeffrey Haessler⁵, Michael H. Preuss⁶, Jin-Fang Chai⁷, Moa P. Lee², Christy L. Avery², Ching-Yu Cheng^{8,9,10}, Nora Franceschini², Xueling Sim⁷, Nancy J. Cox⁴, Charles Kooperberg⁵, Kari E. North^{2,11}, Yun Li^{1,3,12,13} and Laura M. Raffield^{13,14}



RESEARCH ARTICLE

Impact of common genetic determinants of Hemoglobin A1c on type 2 diabetes risk and diagnosis in ancestrally diverse populations: A transethnic genome-wide meta-analysis

Eleanor Wheeler¹⁴, Aaron Leong^{2,34}, Ching-Ti Liu⁴, Marie-France Hivert^{5,6}, Rona J. Strawbridge^{7,8}, Clara Podmore^{9,10}, Man Li^{11,12,13}, Jie Yao¹⁴, Xueling Sim¹⁵, Jaeyoung Hong⁴, Audrey Y. Chu^{16,17}, Weihua Zhang^{18,19}, Xu Wang²⁰, Peng Chen^{15,21,22,23}

Diabetes Care

A Genome-Wide Association Study Identifies Blood Disorder-Related Variants Influencing Hemoglobin A_{1c} With Implications for Glycemic Status in U.S. Hispanics/Latinos

Diabetes Care 2019;42:1784–1791 | <https://doi.org/10.2337/dc19-0168>

Jee-Young Moon,¹ Tin L. Louie,² Deepthi Jain,² Tamar Sofer,^{2,3} Claudia Schurmann,⁴ Jennifer E. Below,⁵ Chao-Qiang Lai,⁶ M. Larissa Aviles-Santa,⁷ Gregory A. Talavera,⁸ Caren E. Smith,⁹ Lauren E. Petty,⁵ Erwin P. Bottinger,⁹ Yil-Der Ida Chen,¹⁰ Kent D. Taylor,¹⁰ Martha L. Daviglus,¹¹ Jianwen Cai,¹² Tao Wang,¹ Katherine L. Tucker,¹³ José M. Ordovás,^{5,14} Craig L. Hanis,⁵ Ruth J.F. Loos,⁵ Neil Schneiderman,¹⁵ Jerome I. Rotter,¹⁰ Robert C. Kaplan,^{1,16} and Qibin Qi¹



Current Diabetes Reports (2018) 18: 52
<https://doi.org/10.1007/s11892-018-1022-4>

GENETICS (AP MORRIS, SECTION EDITOR)

Impact of Genetic Determinants of HbA1c on Type 2 Diabetes Risk and Diagnosis

Chloé Sarnowski¹ · Marie-France Hivert^{2,3}

BMJ Open
Diabetes
Research
& Care

Association of *G6PD* variants with hemoglobin A1c and impact on diabetes diagnosis in East Asian individuals

Aaron Leong,^{1,2} Victor Jun Yu Lim,³ Chaolong Wang,^{4,5} Jin-Fang Chai,³ Rajkumar Dorajoo,⁵ Chew-Kiat Heng,^{6,7} Rob M van Dam,³ Woon-Puay Koh,⁸ Jian-Min Yuan,^{9,10} Jost B Jonas,^{11,12} Ya Xing Wang,¹² Wen-Bin Wei,¹³ Jianjun Liu,^{5,14} Dermot F Reilly,¹⁵ Tien-Yin Wong,^{16,17} Ching-Yu Cheng,^{16,17} Xueling Sim^{15,3}

ARTICLE

Impact of Rare and Common Genetic Variants on Diabetes Diagnosis by Hemoglobin A1c in Multi-Ancestry Cohorts: The Trans-Omics for Precision Medicine Program

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(Author list continued on next page)



Genetic differences $\neq$ Race differences

- Some of the emerging genetic variations associated with hemoglobin and HbA1C vary by race/ethnicity
 - Likely a subgroup, i.e. not ALL Black adults
 - Uncommon genetic variations are likely driving race differences in distributions of hemoglobin and HbA1c in the population
- Conditions that affect red cell turnover, hemoglobin, and/or HbA1c may ***overlap*** with race but are **NOT** race



Key points

- The strong link between HbA1c and complications in both Black and White adults → critical clinical importance for use of HbA1c
- Race is an extremely poor proxy for unknown genetic variation
- Race is not a precise construct; we need to move beyond “race-based analyses” to better understand non-glycemic factors that may be relevant and reduce real disparities in diabetes



Where to go from here?

- More work to understand contribution of non-glycemic factors to HbA1c
 - E.g., ongoing genetics work that relates to hematologic genetic variants
- Race is not a precise construct and a **poor surrogate** for differences in underlying causes of disease risk
 - “Race-based medicine” is disquieting
 - Major causes of disparities in diabetes are not “hematological”



Implications of Racial Differences in HbA1C

- **Current evidence** supports similar interpretation of HbA1c test results across all race and ethnic groups for diagnosis and treatment of diabetes
- Calls for “race-specific” cut-points for diabetes are misguided and draw attention away from real health disparities
 - In the absence of an understanding of the full genetic determinants of HbA1c any “race-specific” approaches will be WRONG
- In the short term and from a pragmatic standpoint, we can use a **combination of fasting glucose and HbA1c to diagnose diabetes** and pay attention to any discordance



HbA1c is a Useful and Valid Test Across Race/ethnic Groups

- Genetic differences $\neq$ Race differences
- Discouraging use of HbA1c in certain race or ethnic groups could worsen diabetes disparities
- For clinical cut-points and medical decision-making, we need to understand underlying causes of group-level differences and focus on objective, biological measures



THANK YOU

