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Do diabetes phenotypes in US women differ by race/ethnicity? A population-based cluster analysis

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ABSTRACT

Objective: US women exhibit racial disparities in the lifetime risk of diabetes and related outcomes. Identifying heterogeneity in clinical presentation may assist with reducing racial disparities in diabetes outcomes. We identified clinical phenotypes of diabetes and examined their racial and ethnic distribution in US women.
Research design and methods: We conducted cluster analysis based on five factors in US women with diagnosed diabetes assessed in the National Health and Nutrition Examination Surveys 1999–2018 (n = 825). Multinomial logistic regression analysis was performed to identify racial and ethnic differences in the distribution of phenotypes.
Results: We identified four distinct clinical phenotypes. Two phenotypes, mild age-related and severe insulin-deficient diabetes, each included approximately a third of women. Mild insulin-resistant and severe insulin-resistant diabetes phenotypes accounted for 19.9% and 13.7%, respectively. The distribution of clusters did not differ by race and ethnicity.
Conclusions: The prevalence of four clinically distinct diabetes phenotypes identified in US women did not differ by race and ethnicity.

1. Introduction

Diabetes is a chronic and debilitating disease affecting 12.0% of US women as of 2019 [1]. People with diabetes may experience different clinical presentations, etiologies, and complications [2]. Racial/ethnic disparities in diabetes prevalence and treatment have been consistently observed [3]. These racial and ethnic disparities are particularly pronounced among women. For example, in 2018–19, the age-adjusted prevalence of diagnosed diabetes was 12.0% in non-Hispanic Black women and 6.6% in non-Hispanic White women [1]. In addition to evidence suggesting considerable gender differences in the pathophysiology and pathogenesis of diabetes [4], data suggest that racial minority women have higher risks of type 2 diabetes and related complications than men [4,5].

Recent studies have proposed the classification of individuals with diabetes based on novel phenotypes using routinely collected data [6,7]. Tailoring diabetes management strategies based on phenotypical presentation may be more effective, leading to lower diabetes-related morbidity and mortality. Developing and assessing the distribution of these phenotypes by race and ethnicity in the US population may assist with more effective diabetes management. We aimed to identify diabetes phenotypes and their race and ethnic distribution in US women given the combination of gendered racial disparities in diabetes and the potential for worse outcomes in women.

2. Methods

2.1. Data and sample

We draw on data from ten continuous waves of the National Health and Nutrition Examination Surveys over 1999–2018 (NHANES). Details of the study design and survey methods are available elsewhere [8]. Each NHANES participant had an in-person home interview and randomly selected adults had detailed physical examinations in a mobile examination center (MEC). A subset of survey participants had fasting blood sampling collected at the MEC after at least 9 h of fasting.

This analysis was restricted to women aged 30–79 who had body mass index [BMI] ≥ 18.5kg/m2 and reported diagnosed diabetes.

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Among women who meet the criteria (n = 9157), we excluded individuals with outliers in biomarkers used in the study (n = 50 cases), resulting in a final sample of 825 women.

2.2. Measurements

Diagnosed diabetes was measured using a survey question asking whether they had ever been told by a doctor or other health professional that they had diabetes. We selected clinical factors relevant to diabetes presentation and management based on previous studies [9]: hemoglobin A1c (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-B), age at diagnosis, and BMI. HOMA-IR was defined as the fasting plasma glucose (mmol/L) × fasting plasma insulin (μU/mL/22.5). HOMA-B was defined as 20 × fasting insulin (μIU/ml)/[fasting glucose (mmol/l) - 3.5]. BMI was calculated using measured height (m^2) and weight (kg). Race/ethnicity was determined by self-reported racial/ethnic information.

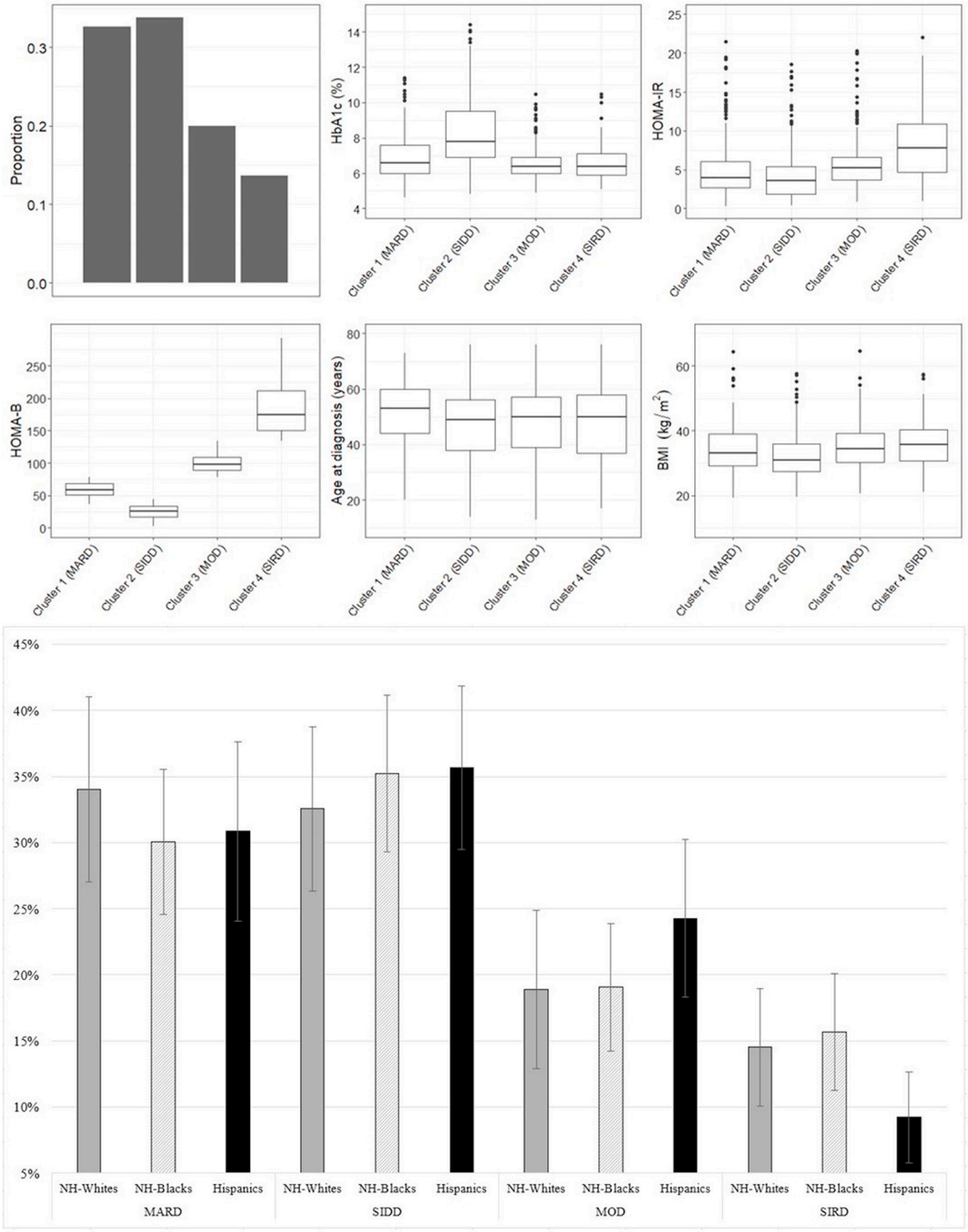

Fig. 1. Proportion of four phenotypes and distributions of clinical factors by four phenotypes (top) and distribution of clusters within each racial/ethnic group (bottom)
NH: non-Hispanic. MARD: mild age-related diabetes. SIDD: severe insulin-deficient diabetes. MOD: mild obesity-related diabetes. SIRD: severe insulin-resistant diabetes
NHANES complex sampling design was accounted for.

2.3. Statistical analysis

We performed the k-medoids method to identify distinct clusters of women with diagnosed diabetes based on five widely-cited risk factors. The k-medoid method uses medians, instead of means used in the k-means algorithm. This reduces potential noise caused by outliers [10]. The same procedure was applied using k-means method and results were very similar (data not shown). The optimal number of clusters in our data was determined based on average silhouette width and elbow method [11]. To assess racial/ethnic differences in clusters, we applied unadjusted and adjusted multinomial logistic regression. All analyses were conducted with R version 4.2.1 [12].

3. Results

Mean age of the analytic sample was 58.5 years and the percentage of non-Hispanic whites, non-Hispanic blacks, and Hispanics was 61.2%, 19.0%, and 19.8%, respectively (Appendix Table A1). Compared to non-Hispanic white women, non-Hispanic black and Hispanic women had significantly higher HbA1c level but showed younger age at diagnosis. Moreover, Hispanic women, compared to non-Hispanic white women, had lower mean BMI and percentage of taking any glucose-lowering agent and having any comorbidity.

Elbow and Silhouette methods in k-medoid for determining the optimal number of clusters suggested four clusters in the sample (Fig. 1). The mild age-related diabetes (MARD) included 32.6% of the analytic sample and was characterized by a relatively old age at diagnosis of diabetes (mean = 51.3 years, 95% CI = 49.5, 53.1), yet low HOMA-IR and HOMA-B levels, and modest BMI. The cluster with severe insulin-deficient diabetes (SIDD) included 33.7% of the sample and this group showed a high level of HbA1c level (mean = 8.3%, 95% CI = 8.0, 8.6%), but relatively lower HOMA-IR, HOMA-B, and BMI. The third cluster had mild obesity-related diabetes (MOD) which included approximately 20% of the sample and this group had relatively high BMI (mean = 35.0, 95% CI = 33.6, 36.4) and moderate HOMA-IR (mean = 5.9%, 95% CI = 5.2, 6.6%) and HOMA-B (mean = 100.2, 95% CI = 97.7, 102.7). The severe insulin-resistant diabetes (SIRD) cluster included 13.7% of the sample and this group had highest average HOMA-IR (mean = 8.3%, 95% CI = 8.0, 8.6%) and HOMA-B (mean = 183.0, 95% CI = 171.3, 194.6). The figure also depicts the distribution of the four clusters by race/ethnicity. There was no significant difference in the distribution, indicating that no racial/ethnic group had higher likelihood of exhibiting a certain phenotype than other racial/ethnic groups.

Table 1 presents results from unadjusted and adjusted multinomial logistic regression analyses. Unadjusted models show that there was no significant difference between racial/ethnic groups in terms of having SIDD, MOD, and SIRD phenotypes relative to having MARD. When demographics and other health risk factors were adjusted for, Hispanic women had an increased risk of having MOD phenotype relative to MARD compared with White women (odds ratio = 2.20, 95% CI = 1.14–4.23).

Table 1
Multinomial regression analysis for diabetes phenotypes among US women with diagnosed with diabetes aged 30–79, NHANES 1999–2018.

		Unadjusted	95% CI	Adjusted	95% CI
		Odds ratio		Odds ratio	
MARD	Non-Hispanic Black	1.00	–	1.00	–
	Hispanic	1.00	–	1.00	–
SIDD	Non-Hispanic Black	1.22	0.79, 1.90	1.16	0.72, 1.85
	Hispanic	1.21	0.73, 1.99	0.99	0.56, 1.76
MOD	Non-Hispanic Black	1.14	0.64, 2.03	1.30	0.72, 2.36
	Hispanic	1.42	0.79, 2.56	2.20	1.14, 4.23
SIRD	Non-Hispanic Black	1.22	0.73, 2.05	1.23	0.71, 2.12
	Hispanic	0.70	0.38, 1.29	0.97	0.46, 2.04

Reference: Non-Hispanic White.
MARD: mild age-related diabetes. SIDD: severe insulin-deficient diabetes. MOD: mild obesity-related diabetes. SIRD: severe insulin-resistant diabetes.

4. Discussion

In this study of nationally representative US women, we identified four diabetes phenotypes based on five clinical markers. Approximately one-third of US women with diagnosed diabetes exhibited high levels of blood glucose and were classified in the SIDD group. Another one-third of women exhibited high insulin resistance and were classified as SIRD. The distribution of phenotypes within each racial/ethnic group was similar, except Hispanic women had a higher likelihood of having MOD phenotype than White women after accounting for demographic and other clinical characteristics. In particular, Hispanic women had a higher chance of having MOD phenotype than white women due in part to Hispanic women's younger age at diagnosis and lower percentage of taking anti-diabetic pills and insulin (Appendix Table A2). This finding suggests that once women develop diabetes, they have different clinical features as well as other cardio-metabolic risks, but their phenotypic presentation of diabetes is very similar across race/ethnicity.

Our results are consistent with previous findings [9]. That is, several cluster analyses obtained four clusters with similar clinical characteristics as those observed in the current study [7,13]. One difference is that previous studies commonly reported SIRD accounts for 8–15% of the study sample, whereas, in our nationally-representative sample, SIRD accounted for about a third of women. This may be because we analyzed women with prevalent diagnosed diabetes instead of individuals newly diagnosed diabetes and, thus, women in our sample might have had diabetes for a longer period which might influence insulin resistance levels. On the other hand, several studies obtained five or more phenotypes of diabetes among people with diabetes [6,14–16]. One cluster frequently proposed in other studies, but not included in our sample, was the severe autoimmune diabetes subtype (SAID). In previous studies, SAID has been found to include a small proportion of the study sample and characterized by early onset of diabetes and shows similar features as SIDD but has a relatively lower HbA1c level [6,16]. This cluster seems not to be identified in our study because our sample includes adult women who are likely to have type 2 diabetes and similar clinical features between SAID and SIDD.

Several limitations of this study should be acknowledged. First, since our study group was women with a previous diagnosis of diabetes, we did not consider those with undiagnosed diabetes. Because racial and ethnic minorities tend to have a higher prevalence of undiagnosed diabetes [17] and undiagnosed diabetes is associated with an increased risk of metabolic syndrome [18], we may underestimate the size of Black and Hispanic women in clusters of mild or severe insulin resistance. Second, although we considered age at diagnosis of diabetes in a clustering analysis, there might be substantial variation in the metabolic factors used in this study by duration of diabetes.

5. Conclusion

We identified four clinically distinct diabetes phenotypes among US women: mild age-related diabetes, mild insulin-deficient diabetes, mild insulin-resistant diabetes, and severe insulin-resistant diabetes. These phenotypes offer new insights on population prevention and management strategies to address diabetes in women. For example, lifestyle prevention and management may be more salient for the ~80% of women who experience mild age-related diabetes and insulin resistant

varieties of diabetes, while medical therapies may be the only recourse for insulin deficient variants. While there were no racial differences in the distribution of diabetes phenotypes, proper identification of diabetes phenotype may assist with clinical management in all race and ethnic groups.

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CRediT authorship contribution statement

Daesung Choi: Writing – original draft, Conceptualization, Methodology, Software. **Rebecca Jones-Antwi:** Data curation, Software. **Mohammed K. Ali:** Writing – original draft. **Shivani A. Patel:** Supervision, Conceptualization, Writing – original draft.

Declaration of competing interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metop.2022.100225.

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