Type 2 Diabetes and Ethnic Disparities in Cognitive Impairment

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Objectives: We explored whether ethnic differences in type 2 diabetes (T2D) explain ethnic disparities in cognitive impairment.

Design: Longitudinal study.

Setting: A cohort study of multiethnic community-dwelling elderly persons in Northern Manhattan, New York.

Participants: 941 participants aged ≥65 years without prevalent cognitive impairment or dementia (CID) were followed for a median of 7.1 years.

Main Outcomes Measures: CID was defined by a clinical dementia rating ≥.5. CID risk attributable to T2D was estimated for each ethnic group using the hazard ratio (HR) relating T2D and CID and the ethnic prevalence of T2D.

Results: 448 participants developed CID; 69 (31.4%) non-Hispanic Whites (Whites); 152 (48.6%) non-Hispanic-Blacks (Blacks); 227 (55.6%) Hispanics, $P<.001$. T2D prevalence was 8.2% in Whites, 20.1% in Blacks, and 19.6% in Hispanics, $P<.001$. Controlling for age, sex, education, and APOE ε4, the HR relating T2D and CID was 1.63 (95% CI 1.26, 2.09). CID attributable to T2D was higher in Blacks and Hispanics compared to Whites (11.4% vs 4.9%; $P=.06$). We estimated that reducing the ethnic disparities in diabetes prevalence could reduce the CID ethnic disparities by 17%.

Conclusions: Reducing ethnic differences in T2D prevalence could partially reduce ethnic differences in incident CID. (*Ethn Dis.* 2012;22(1):38–44)

Key Words: Type 2 Diabetes, Disparities, Cognitive Impairment, Dementia

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Introduction

Epidemiologic studies of the elderly have shown higher prevalence and incidence of dementia in African-Americans[1–12] and Hispanics[3,8,10,13] compared with non-Hispanic Whites (Whites). Type 2 diabetes mellitus (T2D) is also known to be more prevalent in non-Hispanic Blacks (Blacks) and Hispanics compared with Whites.[14] We previously reported that T2D is associated with a higher risk of the major forms of cognitive impairment in the elderly, including Alzheimer's disease (AD),[15–18] vascular dementia,[19,20] amnestic and non-amnestic mild cognitive impairment,[21,22] and cognitive impairment without dementia.[20] Thus, T2D is a risk factor for a wide spectrum of cognitive impairment which we term cognitive impairment or dementia (CID).

Drawing upon these findings, we examined whether the ethnic differences in T2D prevalence could explain the ethnic differences in the incidence of CID in the elderly in Northern New York City. We explored the potential impact on the development of CID of eliminating ethnic disparities in T2D prevalence.

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Methods

Data

Participants and Setting

Analyses included participants from the 1992 longitudinal multiethnic cohort of the Washington Heights-Inwood Community Aging Project (WHICAP), which is a stratified random sample of Medicare recipients aged ≥65 years residing in northern Manhattan, New York City. Procedures for enrollment of patients included in this study have been reported elsewhere.[13] Between 1992 and 1994, all participants underwent baseline assessment, including in-person interviews of general health and function, medical history, physical and neurological examination as well as a neuropsychological battery.[23] Follow-up data were collected in approximately 18-month intervals. Informed consent was obtained from all participants during study enrollment and at each follow-up. The Columbia University Institutional Review Board approved this project.

Data analyzed within this study include patient information through December 2006. Of the 2,125 participants in the study, we first excluded those without follow-up evaluations ($n=737$), then those with prevalent CID at baseline evaluation ($n=408$), and finally those with missing T2D history as part of the baseline medical history ($n=39$). Six participants report-

ed a racial and ethnic group other than White, Black, or Hispanic and were grouped with the White group. Thus, the final sample included 941 participants for the present study. In comparison with the participants analyzed in the current study, those excluded from analysis were older at baseline (median 77.7 years vs 74.0, Kruskal-Wallis test, $P<.0001$) and were more likely to have a history of stroke (14.4% vs 7.3%, $P<.0001$) and heart disease (21.6% vs 15.8%, $P=.003$).

Ascertainment of Medical History

Medical history information was obtained from baseline visit questionnaires and has been described elsewhere.[22] Specifically, determination of T2D was based on self-report, or use of insulin or oral hypoglycemic medications.

APOE Genotyping

We performed APOE genotyping using the method of Hixson and Vernier[24] with slight modification.[25] We included APOE-ε4 as a covariate because it increases the risk of Alzheimer disease[26] and may modify the association between vascular risk factors and CID.[27] We classified persons by presence (homozygeous or heterozygeous) or absence of the APOE ε4 allele; 47 participants in the final sample had missing data on APOE genotype.

Other Covariates

Ethnic group was based on self-report using the format of the 1990 census.[28] Individuals were asked if they were of Hispanic origin; nearly all Hispanic subjects in our cohort were from the Caribbean region. Participants were then assigned to one of three groups: Whites, Blacks, and Hispanics. We examined education both as a continuous variable (years of education completed) and in quartiles (0–6 years, 7–12 years, 13–16 years, and >16 years of education).

Diagnosis of Cognitive Impairment or Dementia (CID)

The diagnosis of CID was established based on information from initial and follow-up assessments. Cognitive diagnosis was determined by consensus at a conference of physicians, neurologists, neuropsychologists and psychiatrists. The diagnosis of CID required evidence of impairment on a neuropsychological test battery with at least mild impairment in social or occupational function (clinical dementia rating ≥.5). This definition of CID includes dementia due to AD,[15–18] vascular dementia,[19,20] amnestic and non-amnestic mild cognitive impairment (MCI),[21,22] and cognitive impairment without dementia (CIND)[20] used by our group in previous analyses and other investigators as well. The rationale for using this broad definition of cognitive impairment was to capture all forms and stages of cognitive impairment, and not just one stage of cognitive impairment (eg, dementia) or one form of dementia (eg, AD). Thus, we sought to explore the entire range of cognitive complications associated with T2D.

Statistical Methods

We compared demographic characteristics and the distribution of risk factors among those who developed CID with those who remained free of CID. Continuous variables were compared using analysis of variance or by non-parametric means when not normally distributed. Categorical variables were compared using chi-squared tests.[29] Cox proportional-hazards regression models[30] were used in multivariate analyses exploring the association of T2D to incident CID. The time-to-event variable was age at diagnosis of CID. Participants who did not develop CID were censored at the time of last follow-up.

Several models examined the association between T2D and CID. After univariate analysis, we sequentially controlled for sociodemographic and other non-modifiable variables. Given that vascular factors such as hypertension, dyslipidemia, and heart disease cluster with T2D[31] and may be in the causal pathway linking T2D with CID,[32] for our final analysis we chose to focus on a model including significant socioeconomic and non-modifiable variables only. We present the following models for the relation between T2D and CID: adjusted for age only (model A), plus sex and education (model B), and additional inclusion of APOE-ε4 status (model C). We used model C for our estimation of population attributable risk (PAR).

Assuming a causal relation of T2D with CID, the risk of CID attributable to T2D can be calculated using the following formula:

$$PAR = p(RR-1)/[1+p(RR-1)]$$

where RR is the adjusted hazard ratio obtained from the multivariate models, and p is the prevalence of T2D[33] for a given ethnic group in this sample.

Based on contingency tables of T2D and CID for each ethnic group (where a=disease and exposure, b=no disease with exposure, c=disease with no exposure, d=no disease and no exposure, and t=total participants), the estimated variance (VAR_i) of the PAR for prospective studies[33] for T2D and cognitive impairment for the ith ethnicity was calculated:

$$\hat{Var}_i = \left[(ct(ad(t-c)+bc^2))\right] / \left[(a+c)^3(c+d)^3\right]$$

The P values examining differences in PAR between ethnic groups were derived from a Z-score, calculated by the following equation:

$$Z = PAR_A - PAR_B / \sqrt{\hat{Var}_A + \hat{Var}_B}$$

SAS version 9.1 was used for all statistical analyses; two-tailed P values from Z-scores for PAR differences were derived from standardized tables for normal curves.

Table 1. Characteristics of the participants included for study (*n*=941)

Characteristics	Overall	Non-Hispanic Whites (*n*=220, 23.4%)	Non-Hispanic Blacks (*n*=313, 33.2%)	Caribbean Hispanics (*n*=408, 43.4%)	*P*
Age, median (IQR)	74.0 (70.4–78.5)	74.8 (71.0–80.2)	74.7 (70.9–79.0)	73.3 (70.2–77.5)	.01[a]
Years of follow-up, median (IQR)	7.1 (3.4–10.2)	5.9 (3.2–9.6)	6.3 (3.3–9.6)	8.4 (3.9–11.0)	<.01[a]
Women, n (%)	657 (69.8)	143 (65.0)	219 (70.0)	295 (72.3)	.16[b]
Years of education, median (IQR)	9 (6–12)	12 (10–15)	10 (8–12)	6 (3–8.5)	<.01[a]
APOE 4/4 or 4/-, *n* (%) (*n*=894)	258 (28.9)	45 (22.5)	111 (37.8)	102 (25.5)	<.01[b]
Diabetes, *n* (%)	161 (17.1)	18 (8.2)	63 (20.1)	80 (19.6)	<.01[b]
Incident dementia, *n* (%)	197 (20.9)	20 (9.1)	75 (24.0)	102 (25.0)	<.01[b]
Incident cognitive impairment or dementia, n (%)	448 (47.6)	69 (31.4)	152 (48.6)	227 (55.6)	<.01[b]

P derived from [a] Kruskal-Wallis Test or [b] Pearson Chi-Square.

Finally, we estimated the potential absolute and relative impact on CID by eliminating ethnic disparities in T2D prevalence. For example, in determining the impact in Whites vs Blacks, first we calculated the difference in PAR between Whites and Blacks. We then multiplied the PAR difference by the observed number of CID cases in Blacks, which provided the expected difference in CID cases, if PARs for Whites and Blacks were equal. We then calculated the new (expected) incidence of CID in Blacks by subtracting the difference in CID cases from the observed number of CID cases in Blacks. Subtracting the Blacks expected from observed CID incidence yielded an absolute CID incidence decrease for Blacks. We calculated the relative CID decrease between Blacks and Whites by dividing the Blacks absolute CID incidence decrease by the difference in CID incidence between Blacks and Whites. We repeated these steps for Whites compared with Hispanics, as well as Whites compared to all others.

RESULTS

Overall 448 patients developed CID over 6652.4 person-years of follow-up (mean 7.1 years [SD 3.9 years]), including 69 (31.4%) Whites, 152 (48.6%) Blacks, and 227 (55.6%) Hispanics. As shown in Table 1, the prevalence of T2D at baseline was 8.2% in Whites, 20.1% in Blacks, and 19.6% in Hispanics, ($P<.01$). Caribbean Hispanics were younger at baseline, had more years of follow-up, less years of education, and a higher incidence of cognitive impairment or dementia compared to Non-Hispanic Whites. Non-Hispanic Blacks had less years of education, a higher prevalence of the APOE-ε4 allele, and a higher incidence of cognitive impairment or dementia compared to Non-Hispanic Whites.

Out of the 448 cases of CID, 197 (43.9%) were dementia and 251 (46.1%) were cognitive impairment without dementia. Of the 197 cases of dementia, 177 (89.8%) were probable and possible AD, 17 (8.6%) were vascular dementia, and 3 (1.5%) cases were other causes such as Lewy body dementia. The 177 cases with possible or probable AD included 12 (6.8%) cases of possible AD with stroke. Out of the 251 cases of cognitive impairment without dementia, 134 (53.4%) met criteria for MCI; 65 (48.5%) of the 134 cases of MCI had amnestic MCI, and 69 (51.5%) had non-amnestic MCI. The 117 cases of cognitive impairment without dementia that did not meet criteria for MCI were considered CIND.

Non-modifiable variables associated with CID in bivariate models ($P<.10$) included age at entry into study, ethnic group, number of years of education (both as a continuous variable and as quartiles), and *APOE-e4*. An interaction term for T2D and ethnicity in relation to CID was not statistically significant ($P=.19$). Thus, we assumed that the relation between T2D and CID was homogeneous across ethnic groups and used the HR for the whole group in calculating the PAR.

Four models for the effect of T2D on incident CID are presented in Table 2. First, a model adjusted only for age which had an HR=1.85 (95% CI=1.46, 2.35) for the relationship between T2D and incident CID. Second, we created a model which additionally included sex and education and yielded a HR=1.70 (95% CI=1.34, 2.16). Our third model additionally included *APOE* genotype and yielded a HR=1.68 (95%CI=1.31, 2.15). Finally a fourth model included each of the variables in the third model plus ethnicity and yielded a HR=1.57 (95% CI=1.23, 2.02).

Table 2. Hazard ratios and confidence intervals from proportional hazards models relating type 2 diabetes to incident cognitive impairment or dementia

Model	*n*	HR (95% CI)
A	941	1.85 (1.46, 2.35)
B	941	1.70 (1.34, 2.16)
C	894	1.68 (1.31, 2.15)
D	894	1.57 (1.23, 2.02)

Model A: unadjusted.
Model B: model A plus sex and number of years of education (quartiles).
Model C: model B plus APOE ε4 status.
Model D: model C plus ethnicity.

Table 3. Population attributable risk (and 95%CI) for diabetes leading to cognitive impairment by ethnicity using hazard ratios derived from models outlined in Table 2

Model	Non-Hispanic White	Non-Hispanic Black	*P* Blacks vs Whites	Caribbean Hispanic	*P* Hispanics vs Whites	All minority subjects	*P* minority vs Whites
A	6.52 (.59, 12.44)	14.59 (8.87, 20.32)	.05	14.28 (10.03, 18.53)	.04	14.41 (10.96, 17.85)	.02
B	5.43 (−.50, 11.35)	12.33 (6.61, 18.06)	.10	12.06 (7.82, 16.31)	.08	12.17 (8.73, 15.62)	.05
C	4.85 (−.78, 10.49)	11.65 (5.80, 17.49)	.10	11.31 (7.17, 15.44)	.07	11.44 (8.02, 14.86)	.06
D	4.10 (−1.54, 9.74)	9.95 (4.11, 15.80)	.16	9.66 (5.52, 13.79)	.12	9.77 (6.35, 13.19)	.10

Model A: adjusted for age (as timescale).
Model B: model A plus sex and number of years of education (quartiles).
Model C: model B plus APOE-ε4 status.
Model D: model C plus ethnicity.

For our analysis of PAR we chose to use the model which included T2D, sex, education, and APOE ε4 status with age at CID as the time-to-event variable (model C). The sample size available for analysis in this group was 894. The comparison of PARs of Blacks and Hispanics individually vs Whites was close to statistical significance (P=.10 and P=.07 respectively). (Table 3)

Given that prevalence of T2D and the PAR of CID for Blacks and Hispanics were similar, we compared Whites vs combined Blacks or Hispanics and the difference in PAR was closer to statistical significance (P=.06). If the relation between T2D and CID were causal, our attributable risk analysis demonstrates that eliminating ethnic disparities in T2D could reduce the absolute incidence of CID in minority patients by 3.5% and the relative difference in CID incidence between Whites and all other patients would decrease by approximately 17% (Table 4).

DISCUSSION

In our study we have shown that eliminating the ethnic disparities in the prevalence of T2D may have a meaningful impact on decreasing the ethnic disparities in CID. Our group previously reported that the incidence of AD was higher in Blacks and Hispanics compared with Whites.[10] We also reported that T2D prevalence was higher in Blacks and Hispanics compared with Whites,[20] and that T2D was associated with a higher risk of several forms of cognitive impairment, including amnestic and non-amnestic MCI,[22] cognitive impairment without dementia,[20] AD,[20,34] and vascular dementia.[19,20] A plausible explanation for the increased frequency of dementia among Blacks and Hispanics is over-representation of risk factors for dementia and cerebrovascular disease among minority groups. Minority populations in the United States have disproportionately high prevalence of vascular risk factors, either by clustering,[35] or alone, including T2D,[36–38] hypertension,[36,39,40] cardiovascular disease,[41] and cerebrovascular disease.[42] Several vascular risk factors[32] including T2D,[17,18,43–45] hyperlipidemia,[46] hypertension (HTN),[47] atrial fibrillation,[48] smoking,[18,49–51] hyperhomocysteinemia,[52] and obesity,[53–57] have been associated with the development of dementia, including Alzheimer disease and vascular dementia. Most of these risk factors are potentially modifiable, and interventions targeting dementia risk factor disparities could decrease the relative risk of dementia in minorities. We chose to explore T2D and not other risk factors because T2D is consistently associated with all major forms of cognitive impairment we have explored, whereas other risk factors are not. In

We have shown that eliminating the ethnic disparities in the prevalence of T2D may have a meaningful impact on decreasing the ethnic disparities in CID.

Table 4. Calculation of absolute and relative decrease in disparities in cognitive impairment and dementia if the prevalence of diabetes in Blacks and Hispanics was equalized to that of non-Hispanic Whites

Eq#	Equation name	values
(1)	CID incidence (from Table 1)	379/721 (52.6%)
(2)	CID incidence difference	21.2%
(3)	PAR difference	6.59%
(4)	CID cases difference	25
(5)	Projected CID cases	354
(6)	New CID incidence	354/721 (49.1%)
(7)	Absolute CID incidence decrease	3.5%
(8)	Relative CID incidence decrease	16.5%

addition, T2D has the most appreciable ethnic differences, being twice as prevalent in Blacks and Hispanics compared with Whites. Our results suggest T2D may explain some of the ethnic disparities in CID, and we showed how reducing T2D ethnic disparities could decrease CID disparities. It is important to point out that a causal relation between T2D and CID has not been definitively established. However, there is increasing evidence that T2D is associated with multiple forms of cognitive impairment through biologically plausible mechanisms that include cerebrovascular disease and processes that may affect the amyloid cascade.[58–61] It is also possible that the relationship of T2D and CID and the ethnic differences could be explained by residual confounding. Table 1 showed differences between the racial and ethnic groups in addition to the differences in T2D, particularly for years of education. Caribbean Hispanics and Non-Hispanic Blacks had lower years of education compared to Non-Hispanic Whites. Lower educational attainment is related independently to both a higher risk of T2D[62–66] and a higher risk of CID.[67] Our results were robust even after adjustment for education, but years of education may not appropriately capture ethnic differences in quality of education.[68] Other measures such as reading ability seem to capture ethnic differences in quality of education better than years of education, and adjusting for reading ability may attenuate ethnic differences in CID.[68]

The main limitation of our study is ascertainment of T2D by self-report. Without glycemic measures we could not ascertain undiagnosed T2D or glucose intolerance. This likely resulted in underestimation of T2D prevalence. Thus, it is likely that our findings underestimate the true association between T2D and CID. Type 2 diabetes prevalence was appreciably higher in our study compared with others examining the association between T2D and cognitive impairment, which may raise the issue of sampling bias. However, the high T2D prevalence in our study is explained by the fact that T2D prevalence is twice as high in African Americans and Hispanic elderly,[69,70] who comprised the majority of our sample in contrast to other predominantly non-Hispanic white cohorts.[43,44] The prevalence of self-reported T2D has increased at a 3-fold faster rate in minorities than in Whites.[71] Thus, the high T2D prevalence in our sample is not unexpected and is in line with national survey estimates.[14] Compared with the Third National Health and Nutrition Examination Survey, the prevalence of T2D in our sample was lower in Whites (8% vs. 12%) and Hispanics (19.6% vs. 24%), and very similar in African Americans (20.1% vs. 21%).[14] Most T2D data in Hispanics from national surveys pertain to Mexican-Hispanics. Our study is one of a few with T2D data in Caribbean-Hispanics.

Another relative limitation is that the differences in PAR did not reach the usual *P* of .05. However, *P* values of .1 are commonly considered significant in the social sciences, and the marked ethnic differences in the prevalence of T2D and CID are self-evident in our data, known from previous reports, and unlikely to be due to chance. We grouped together Blacks and Hispanics. The rationale for doing this is that we found no evidence that ethnic group modified the relation between T2D and CID, and that the disparities in CID and T2D between Blacks and Whites, and Hispanics and Whites, were very similar. The fact that the disparities for Blacks and Hispanics were similar may suggest that the differences between Whites and minorities may be mostly reflective of socioeconomic differences and not biologic or genetic differences, although we can only speculate in this regard.

Another potential study limitation is our definition of CID. The main goal of our study was to capture the impact of T2D on all forms of cognitive impairment, rather than one particular form. Thus, we used the most inclusive definition of CID based on previous findings. It is possible that some cases of CDR=.5 do not have significant cognitive impairment and were misclassified. To the extent that this misclassification was random it would have resulted in underestimation of the relation between T2D and CID, thus resulting in an underestimation of the PAR.

The main implication of our findings is that reducing ethnic disparities in T2D prevalence may partially reduce ethnic disparities in incident CID.

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