

Geographical Differences in the Occurrence of Alzheimer's Disease Mortality: United States Versus Puerto Rico

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Since the implementation of the 10th International Classification of Disease in 1999, the trend in Alzheimer's disease mortality rate has not been reported. Here, the age-adjusted Alzheimer's disease mortality rate in Puerto Rico and United States from 1999 to 2004 was analyzed. The results showed an increasing trend in Alzheimer's disease mortality rate in both the United States and Puerto Rico. However in Puerto Rico, the Alzheimer's disease mortality rate (32.4/100 000) was higher than that observed in United States (20.9/100 000). Interestingly, the Alzheimer's disease mortality rate of Puerto Ricans living in Puerto Rico is much

higher than Puerto Ricans living in the United States. The higher occurrence of Alzheimer's disease mortality in Puerto Rico versus the United States could be explained by factors such as coding practices, genetics, socioeconomics, and health care. These results highlight the need for comprehensive studies on factors that may influence diagnosis, death certificate coding practices, and development of Alzheimer's disease pathology in different geographical regions.

Keywords: Alzheimer's disease; tauopathy; Hispanics; epidemiology; mortality rate

Introduction

Alzheimer's disease (AD) is a progressive neurological disorder characterized by loss of memory.¹ This neurological disease affects more than 18 million people worldwide today and this number is expected to double worldwide by year 2025.² Owing to the lack of effective treatments, the number of new AD cases could rise close to 1 million per year by 2050.² In the United States, there are 4.5 million

people with AD and the cost associated with the treatment of these patients is calculated at \$100 billion annually.³ The projected increase in AD cases and the lack of treatments directed to impede or prevent neurodegeneration process have propelled research directed toward the understanding of all factors, from demographics to molecular pathology, associated with development of this insidious neurological disorder.

The greatest risk factor for developing AD is age. The age of onset is 60 years or older and the prevalence doubles every 5 years to the point that almost half of those older than 85 years develop AD.² Owing to the increase on life expectancy in developing countries, the population of people older than 60 years should double by year 2030. Therefore, the number of people at risk of developing AD will increase. In addition to age, genetics has been identified as a contributing factor for the development of AD. Specific mutations in familial cases of early-onset AD were identified at the end of 1980s and the beginning of 1990s.⁴⁻⁶ The identified mutations are

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found predominantly in 3 genes—*APP*, *PSEN1*, and *PSEN2*. However, familial early-onset AD accounts for just a small fraction of all reported cases of AD. Other genes have been correlated to the development of AD. A variant of the gene that encodes the apolipoprotein E (ApoE) protein was identified as genetic risk factor for late-onset AD.^{6,7} Recently, specific variants of other gene, named *SORL1*, have been associated with AD.⁸ The occurrence of the variants of these 2 genes has been studied in different ethnic groups.^{9,10} However, these variants have not been directly correlated to differences in the incidence of AD among ethnic groups, as other contributing factors may play an important role.⁹⁻¹³

Several studies suggest that there are differences in the incidence of AD among ethnic and racial groups.^{13,14} However, no significant differences in prevalence and incidence rates of AD were reported by Fillenbaum and coworkers.¹⁵ Some incidence studies have shown a higher frequency of AD among women, though this trend could be explained by differences in life expectancy between women and men.^{16,17} Overall, the results remain highly controversial to determine whether gender, race, and ethnicity have a direct influence in the incidence of AD. The mortality rate associated with AD has been used to determine demographic and risk factors associated among the US population.¹⁸ Conversely, the occurrence of AD mortality in the population of Puerto Rico has been understudied. In this report, we investigated the occurrence of AD mortality from 1999 to 2004 in Puerto Rico, and compared the mortality rates to those in the United States. The year 1999 was the first year that the 10th International Classification of Disease (*ICD-10*) was implemented, so that data from 1999 to 2004 are comparable, but mortality data before 1999 (*ICD-9* and earlier) may not be comparable. To our knowledge, there have been no data published comparing the occurrence of AD mortality in Puerto Rico and the United States since the advent of the *ICD-10*.

Methods

Numerator data for the number of deaths were obtained from the National Center for Health Statistics (NCHS) multiple cause-of-death public-use data files. Numerator data for the United States and Territories (including Puerto Rico) were obtained for 1999-2004. Deaths due to AD (*ICD-10* G30) either as the underlying cause of death or as one of the multiple cause-of-death listings in the entity axis

format were used in this analysis.¹⁹ Mortality rates were calculated using data from the US Census Bureau as denominators. Annual estimates of age and sex-specific populations were taken from intercensal population estimates and 2000 US Census data.¹⁹⁻²⁵ All mortality rates were standardized to the 2000 US population via direct standardization using 5-year age groups.

The distribution of AD mortality per region in Puerto Rico was developed using data from the Department of Health of Puerto Rico from 2000 to 2004. The age-adjusted AD mortality rate was calculated and standardized to the 2000 US population for the 2000-2004 period. The map was developed using the Geographic Information System, Manifold version 8.

Results

Alzheimer's disease mortality is higher in Puerto Rico than the United States

Alzheimer's disease occupied the 14th position among the leading underlying causes of deaths in Puerto Rico by 1999. In 2004, AD was the fifth leading underlying cause of death in Puerto Rico. To understand these drastic rate changes in deaths associated with AD in Puerto Rico, the age-adjusted AD mortality rate was calculated for the period of 1999-2004 (Table 1 and Figure 1A). The age-adjusted AD mortality rate for 1999 in Puerto Rico was 21.2 for every 100 000 habitants (Figure 1A). This number increased in the subsequent years, reaching 32.4 deaths for every 100 000 habitants by 2004 (Figure 1A; 95% CI 30.4-34.4). This result indicates a 52.8% increase in the occurrence of AD mortality in 5 years among Puerto Ricans living in Puerto Rico. Conversely in the United States, the age-adjusted AD mortality rate for 1999 was 15.9 per every 100 000 habitants (Figure 1A). As observed in Puerto Rico, the mortality rate associated with AD increased in the United States reaching 20.9 deaths per every 100 000 habitants by 2004. This represents a 31.4% increase in the occurrence of deaths associated with AD for the 5-year period in the United States.

The same patterns seen for the entire population are seen for men and women separately (Table 1 and Figures 1B and 1C). In 1999, the AD mortality rate for women in Puerto Rico was 22.9 for every 100 000 habitants while for the same year in the United States the mortality rate was 16.7 for every 100 000 habitants. In United States and Puerto Rico, an increase was registered for the 5 years (1999-2004) studied,

Table 1. Age-adjusted AD Mortality Rate^a

Year	USA ^b			PR ^b		
	All	F	M	All	F	M
1999	15.9	16.7	13.9	21.2	22.9	18.8
2000	17.6	18.5	15.3	23.8	24.2	23.1
2001	18.5	19.5	16.0	25.7	26.8	24.2
2002	19.6	21.0	16.7	27.8	29.5	25.4
2003	20.6	22.0	17.4	29.3	30.9	27.1
2004	20.9	22.4	17.5	32.4	34.5	29.1

Abbreviations: AD, Alzheimer's disease; F, female; M, male; PR, Puerto Rico; USA, United States of America.

^a Underlying cause of death.

^b 2000 US Standard/100 000.

reaching 22.4 in the United States and 34.5 in Puerto Rico by 2004. This represented an increase in the occurrence of women mortality of 34.1% in the United States and 50.6% in Puerto Rico. The same trend was observed for men, where the AD mortality rate for men was higher in Puerto Rico than in the United States. The occurrence of AD mortality for men in Puerto Rico had a 54.8% increase from 1999 to 2004, whereas in the United States the increase was 25.5% for the same period (Figure 1C).

Alzheimer's disease mortality increased in comparison to other causes of deaths

The mortality rate for all causes of deaths was calculated and compared to AD mortality in United States and Puerto Rico (Figure 2). Figure 2 shows that AD mortality rates in Puerto Rico and the United States increased at the same time as the overall mortality rate was sharply decreasing. The increase in the occurrence of AD mortality may be related to an increase in life expectancy due to survival of other diseases and increments in the 65 years or older population.

Alzheimer's disease as multiple cause of death in the United States and Puerto Rico

Many death certificates list AD as a secondary cause of death rather than the underlying cause. Table 2 and Figure 3 show that in 2004 the multiple-cause AD mortality rate in Puerto Rico was 50% higher than the underlying cause rate; a similar difference (53%) was seen for the United States.

The analysis of AD as a multiple cause of death showed the same trends as underlying cause rates, with higher rates in Puerto Rico compared to the

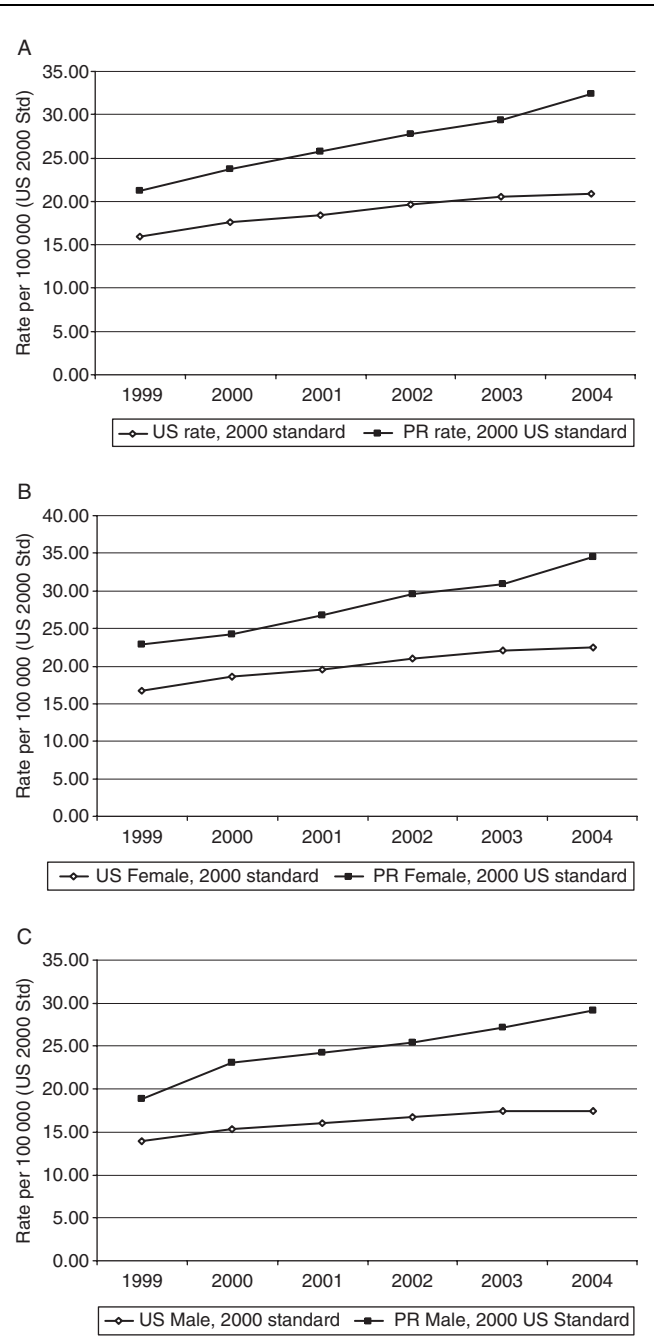


Figure 1. Alzheimer's disease (AD) as underlying cause of death in Puerto Rico (PR) versus the United States (US). A, The AD mortality as underlying cause of death was calculated from 1999 to 2004. The age-adjusted AD mortality rates for the United States (open diamonds) and Puerto Rico (closed squared) was plotted for the 5-year period. The difference in AD mortality based on gender was also analyzed. B, Females in the United States and Puerto Rico showed an increasing trend in AD mortality rate from 1999 to 2004. C, In the case of males, the same increasing trend was observed in the United States and Puerto Rico. In all cases, AD mortality rate is higher in Puerto Rico than in the United States. Std, standardized.

United States and with a greater increase over time. In the United States, AD as multiple cause of death

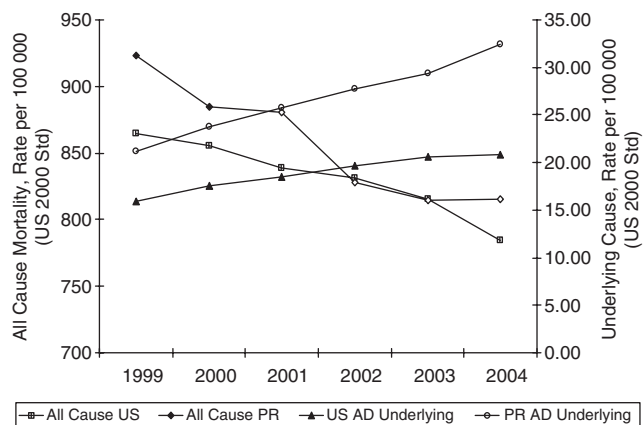


Figure 2. Alzheimer’s disease (AD) versus other causes of death in Puerto Rico (PR) and the United States of America (USA). The mortality rate for all causes of death in the United States (closed square) and Puerto Rico (open diamonds) calculated for the period of 1999-2004 was plotted. The graphs showed a decreasing tendency for both the United States and Puerto Rico. In comparison, AD mortality rates increase for the United States (closed triangle) and Puerto Rico (open circle) during the same period. Std, standardized.

Table 2. Multiple-cause Age-adjusted AD Mortality Rate

Year	USA ^a			PR ^a		
	All	F	M	All	F	M
1999	28.2	28.8	26.2	30.5	32.9	27.2
2000	29.9	30.7	27.8	33.9	34.1	33.4
2001	30.4	31.4	27.8	37.6	39.6	34.8
2002	32.0	33.3	29.0	40.4	43.8	35.5
2003	32.3	33.6	29.0	43.2	45.4	39.9
2004	32.0	33.5	28.7	48.5	50.5	45.5

Abbreviations: AD, Alzheimer’s disease; F, female; M, male; PR, Puerto Rico; USA, United States of America.

^a 2000 US Standard/100 000.

showed an increase of 13.6% from 28.2 per every 100 000 in 1999 to 32.0 in 2004 (Table 2 and Figure 3A). Alzheimer’s disease as multiple cause of death in Puerto Rico increased 59.0%, from 30.5 per every 100 000 in 1999 to 48.5 by 2004 (Table 2 and Figure 3A). Similar patterns were seen for both women and men (Figures 3B and 3C).

Alzheimer’s disease mortality rate of Puerto Ricans in the United States versus Puerto Rico

The census of 2000 reported 3.8 million Puerto Ricans living in Puerto Rico and, practically, the same

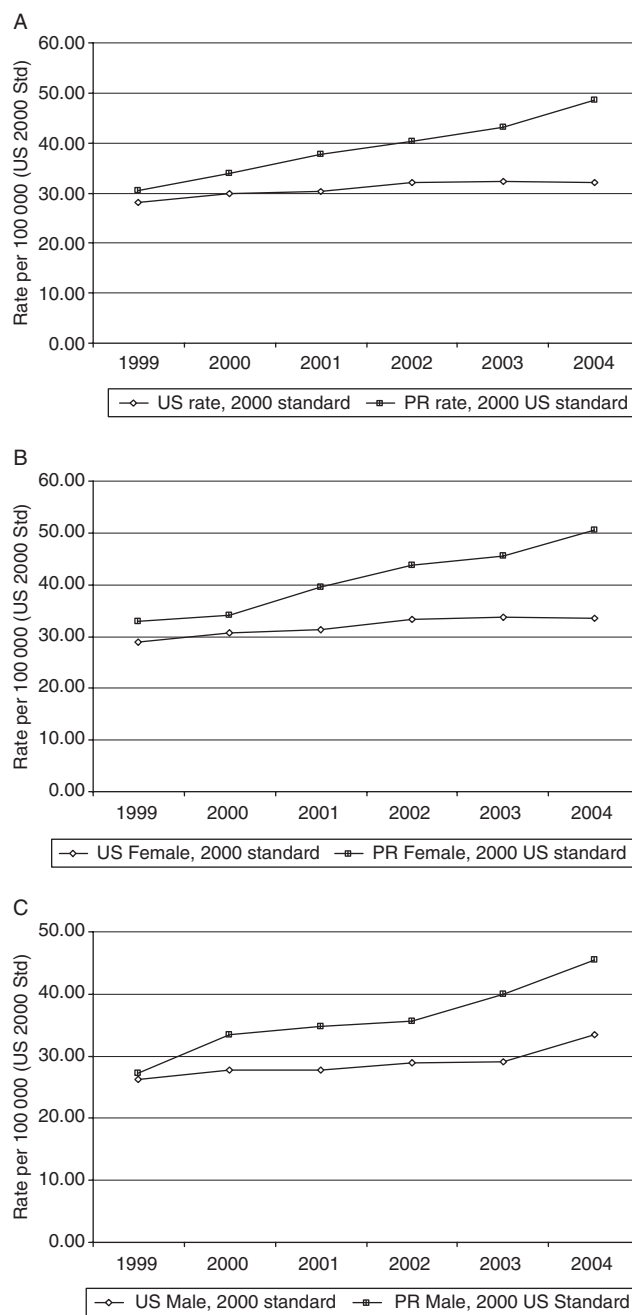


Figure 3. Alzheimer’s disease (AD) as multiple cause of death in Puerto Rico (PR) versus the United States (US). A, The AD mortality as multiple cause of death was calculated from 1999 to 2004. The age-adjusted AD mortality rate in the United States (open diamonds) and Puerto Rico (closed squared) was plotted for the 5-year period. B, Females in the United States and Puerto Rico showed an increasing trend in AD mortality as reported as multiple cause of death from 1999 to 2004. C, In the case of males, the same increasing tendency was observed in the United States and Puerto Rico. Std, standardized.

number of Puerto Ricans living in the United States (3.4 million). The AD mortality for Puerto Ricans in Puerto Rico was of 23.7 per every 100 000 habitants

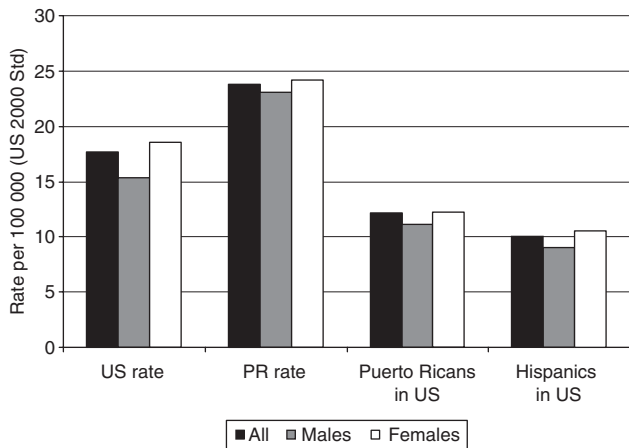


Figure 4. Alzheimer's disease (AD) mortality rate of Puerto Rican in Puerto Rico (PR) versus the United States (US). The age-adjusted AD mortality rate as underlying cause for Puerto Ricans living in Puerto Rico versus the United States was compared. The graph showed the overall AD mortality (black bar), female mortality (lined bar), and male mortality (white bar) for the United States, Puerto Rico, Puerto Ricans living in the United States, and Hispanics living in the United States, as indicated. The differences in AD mortality among Puerto Ricans living in Puerto Rico and United States are statistically significant ($P < .0001$). Std, standardized.

while Puerto Ricans living in the United States, it was 12.1 for the year 2000 (Figure 4; $P < .0001$). Puerto Ricans living in the United States, however, had a similar mortality rate to all Hispanics in the United States (Figure 4).

Regional differences in AD mortality in Puerto Rico

We also calculated the occurrence of AD mortality for the 8 health regions in the island (Figure 5). The 2 regions on the northwest part of the island showed a higher AD mortality rate, while the northeast showed the lowest AD mortality. The southeast region VI (Caguas) also showed a high AD mortality rate. The regions with the lowest AD mortality, Metro and Mayagüez, had a rate closer to that observed in the United States for the same period (Table 1 and Figure 5). Meanwhile, the southern region of Ponce showed a moderate AD mortality rate, but still higher than the one observed in the United States (Figure 5).

Discussion

Alzheimer's disease cases are expected to more than double by year 2025.² This projected increase is due

to the lack of effective treatments that prevent or hinder the neurodegenerative process associated with the development of AD. The pathobiology of AD has been extensively studied. At the molecular level, it has been identified 2 neuronal lesions (senile plaques and neurofibrillary tangles) as pathological hallmarks of AD.^{5,6} The molecular mechanism leading to the formation of these pathological lesions is still unclear. However, several lines of evidence suggest that genetic factors may play a crucial role in the etiology of AD.^{5,6} Ethnicity has been correlated with propensity to develop AD. Some epidemiological studies indicated that African Americans and Hispanics are more likely to develop AD than Caucasians.^{9,10,13,14} The propensity to develop AD has been attributed to the high prevalence of diseases identified as risk factors in these ethnic groups. However, the correlation between ethnicity and AD remains controversial.²⁶

Hispanics in the United States are classified as those people that speak Spanish and/or are descendants of members of this group. The most representative members of the Hispanic population in the United States are Mexicans, Puerto Ricans, and Cubans. Puerto Ricans are the second largest group among Hispanics. In this report, the age-adjusted AD mortality of Puerto Ricans living in the United States and Puerto Rico was analyzed. The occurrence of AD mortality in Puerto Rico is higher than in the United States from 1999 to 2004. For this 5-year period in Puerto Rico, AD mortality rate increased 52.8% while in the United States there was a 31.4% increase. Even though the occurrence of AD mortality was higher in Puerto Rico than in the United States, in both geographical areas women were 1.2 times as likely to die of AD as men. This suggests that there are commonalities in the trend of AD mortality rates in both geographical regions. However, differences in death certificate coding practices and diagnosis criteria cannot be excluded as contributing factors for the higher occurrence of AD mortality in Puerto Rico versus the United States. Additionally, increased awareness or enhanced training of health care providers may also contribute to an increase in reporting AD as an underlying cause of death. These factors are difficult to control in a study that involves the general population. Nevertheless, the analysis of death certificate records represents the appreciation, occurrence, and contribution of a particular disease to the mortality rate in a specific population at a specific time.

Alzheimer's disease reported on the death certificate as multiple cause of death was also analyzed.

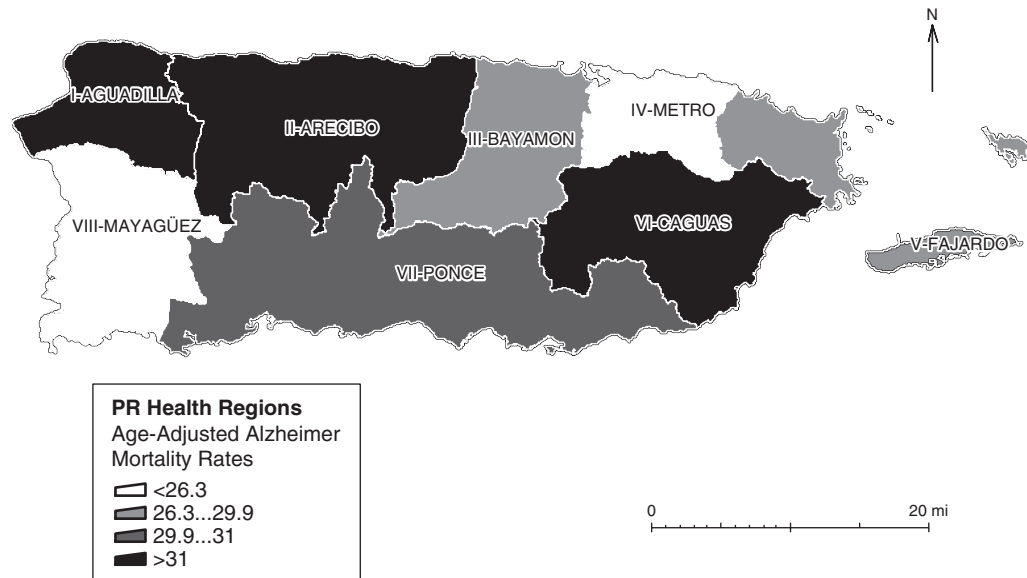


Figure 5. Geographical distribution of Alzheimer's disease (AD) mortality rate in Puerto Rico. The island of Puerto Rico is divided into 8 regions. The regions are illustrated on the map. The legend indicates the ranges of AD mortality rate distributed on the map.

In both the United States and Puerto Rico, AD mortality rate as multiple cause of death increased for the 5-year period. The results showed that by 2004 the multiple-cause AD mortality rate in Puerto Rico was about 50% higher than the underlying cause rate. Consistently, the same phenomenon is observed in United States. Therefore, the increase on AD mortality rate in Puerto Rico is not due to overreporting of AD as underlying cause of death versus secondary cause of death on PR death certificates. Furthermore, while all causes of deaths in the United States and Puerto Rico had declined from 1999 to 2004, age-adjusted AD mortality rate increased. These results suggest that the decrease of mortality rate for other causes of deaths, such as cancer and hypertension, may contribute to the observed increase in the elderly population, which have the highest risk of developing AD.

The population of Puerto Ricans in Puerto Rico and the United States is about the same. In Puerto Rico, there were approximately 3.8 million habitants for the year 2000, while in United States there were 3.4 million. To access AD mortality of Puerto Ricans in different geographical regions, AD mortality as underlying cause of death was analyzed in Puerto Rico versus the United States. We found that the AD mortality rate of Puerto Ricans was higher in Puerto Rico than the United States for the year 2000. The AD mortality rate for Puerto Ricans in Puerto Rico was almost twice as much as that of Puerto Ricans in the United States (23.7 vs 12.1 per

every 100 000 habitants; $P < .0001$). The significant differences in AD mortality rate of Puerto Ricans living in Puerto Rico versus the United States suggest that in addition to genetic differences there may be environmental and social contributing factors. However, the difference could also be attributed to differences in the death certificate coding practices between the Puerto Rico and the United States.

To further understand the observed phenomenon in Puerto Rico, AD mortality rate was analyzed by regions. This analysis demonstrated that the northwest regions of Puerto Rico reported the highest occurrence of AD mortality. Conversely, the northeast (metropolitan area) and southwest (Mayagüez) reported the lowest AD associated mortality in Puerto Rico, which are comparable to that observed in the United States. Geographical variation in AD mortality rate has also been reported in the United States for the period of 1990-1996.²⁶ The geographical differences could be due to underlying causes ranging from access to preventive medicine and good medical care to unknown risk factors. Comparison of population growth for the period of 1999-2004 indicated that the population of 60 years or older increased 7.9% in the United States while in Puerto Rico the increase was 12.3% (data not shown). Interestingly, all age groups in the United States showed an increase of approximately 7.0% for the period. However in Puerto Rico, the population of 29 years or younger showed a decrease of 2.9% suggesting an aging tendency of the population in Puerto Rico

for the period (data not shown). This aging tendency of the population in Puerto Rico may influence the diagnosis or reporting of AD. Thus, the results could be due to geographical difference in the way AD is diagnosed or reported as cause of death. Nevertheless, this report provides the first evidence for an increasing trend in the reporting of AD mortality in Puerto Rico versus the United States.

Our results are based on what was reported on death certificates and not on incidence or prevalence data in Puerto Rico. To our knowledge, there have been no studies of the incidence or prevalence of AD among Puerto Ricans living in Puerto Rico. Such studies would be very useful, although they would require careful attention to a standard method of diagnosis. Analogously in this study, some of our findings could be due to differences in diagnosing AD or in reporting AD as cause of death by the physician that filed the death certificate. Nevertheless, the results showed an increasing trend in AD mortality rate in both the United States and Puerto Rico. The results also show that AD rates were higher among Puerto Ricans living in Puerto Rico versus United States rates, and much higher than rates among Puerto Ricans living in the United States. These results expose the need to identify genetic, environmental, and/or social factors that contribute to the higher AD mortality rate of Puerto Ricans living in Puerto Rico versus those in United States.

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