Epidemic of end-stage renal disease in people with diabetes in the United States population: Do we know the cause?

CAMILLE A. JONES, ANDRZEJ S. KROLEWSKI, JOHN ROGUS, JAY L. XUE, ALLAN COLLINS, and JAMES H. WARRAM

Section on Genetics and Epidemiology, Research Division, Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts; and Minnesota Medical Research Foundation, Minneapolis, Minnesota

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Background. The number of individuals initiating renal replacement therapy in the United States population grew exponentially over the past two decades. Cases of end-stage renal disease (ESRD) attributed to diabetes accounted for most of this increase. In this report we examined factors that may account for the increase to determine whether it truly represents an epidemic of ESRD due to diabetes.

Methods. We reviewed time trends in data of the United States Renal Data System, the Diabetes Surveillance Program of the Centers for Disease Control and Prevention, and diabetes literature.

Results. Recent growth of the number of individuals with diabetes accounted for less than 10% of the increase in the number of diabetes-related ESRD. Instead, most of it was due to a threefold increase in risk of ESRD in people with diabetes and, therefore, qualifies as an epidemic. Curiously, this epidemic occurred despite widening implementation of effective renoprotective therapies. Individuals with type 2 diabetes, regardless of gender, age, or race, experienced the greatest increase in risk. There is no evidence that diabetic patients have been surviving longer, so the increased risk was not attributable to the high risk associated with long duration diabetes.

Conclusion. We hypothesize that an epidemic of ESRD has occurred in people with diabetes in the United States population over the last two decades. The nature of the factor responsible for the epidemic and the reasons it affects patients with type 2 diabetes particularly are unknown. Research efforts to identify the putative factor deserve high priority, as does a commitment of resources to provide care for the burgeoning number of patients with ESRD and type 2 diabetes.

The United States Renal Data System (USRDS) is a roster of individuals accepted for renal replacement therapy in the United States [1–3]. It contains information on nearly 94% of individuals who have initiated renal replacement therapy since 1976 [2]. The primary goals of the USRDS are to provide a description of the populations initiating or continuing on renal replacement therapy, as well as assessments of its effectiveness [2, 4]. USRDS data have been used to evaluate mortality according to modality of renal replacement therapy or specific components of dialysis equipment [5, 6]. In this report we demonstrate how the USRDS data on individuals with newly diagnosed ESRD, combined with estimates of the size of the population with diabetes, can be used to evaluate trends in the occurrence of ESRD in the diabetic population in the United States and to examine possible determinants of the epidemic of ESRD in this population.

DATA BASES AND METHODS

We obtained the number of individuals initiating treatment for ESRD according to cause for the years 1980 through 1999 from the RenDER system of the USRDS (http://www.usrds.org). The number of persons with diagnosed diabetes in the United States according to age, gender, race, and calendar year were obtained from the Diabetes Surveillance Program of the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/diabetes/statistics/index.htm) and projections of the numbers up to 2050 were adapted from a recent publication [7]. Incidence rates (per 100,000 persons with diabetes) of the initiation of treatment for ESRD related to diabetes were computed by CDC according to the same age, gender, and race categories for the years 1984 through 1996 using 3-year rolling averages of the number of persons initiating ESRD treatment (supplied by USRDS) and the number of persons with diagnosed diabetes (Chapter 8, 1999 Diabetes Surveillance Report) (http://www.cdc.gov/diabetes/statistics/index.htm).

Time trends in age- and race-specific incidence rates (and gender-specific rates for persons <45 years of age) between 1984 and 1996 were evaluated by regression
methods, giving the incidence rates equal weight. For all age-, race-, and gender-specific categories of the population, a linear term was sufficient to summarize the trend. Differences between slope parameters were evaluated in analysis of covariance models (SAS version 8 PROC GLM; SAS Institute, Inc., Cary, NC, USA) with indicator variables for group and interaction terms for differences in slopes.

The SAS PROC FORECAST (SAS Institute, Inc.), which includes extrapolative forecasting methods for time series historic data, was used to project the number of new cases and prevalent cases of ESRD attributed to diabetes in the United States to 2010. The historic data were the number of new onset and prevalent cases from 1982 to 2000. We projected each age group independently by using the stepwise autoregressive method, which combines time trend regression with an autoregressive model. We also used exponential smoothing and trending to produce a time trend projection [8].

RESULTS

Increasing number of individuals with new onset ESRD is primarily due to diabetes

The number of individuals initiating treatment for newly diagnosed ESRD in the United States population grew dramatically over the past two decades. During 1982 the number was 22,069. That number doubled (48,353) by 1990 and nearly doubled again (89,318) by 1999. The exponential nature of this increase was accounted for by cases of ESRD attributed to diabetes and hypertension (Fig. 1), while cases attributed to glomerulonephritis or other causes increased only gradually. In the late 1980s and in the 1990s, the rate of increase for hypertension-related cases of ESRD abated somewhat, but the steep rate of increase for diabetes-related cases of ESRD has continued unabated.

Can this increase be due to changes in the assignment of causes of ESRD?

Admittedly, recent attention to diabetes may have increased the inclination of doctors to list diabetes as the primary cause of ESRD when another cause, such as hypertension, was also present. However, already in the 1980s, almost all ESRD patients with both hypertension and diabetes were classified as having ESRD due to diabetes [9], so a large increase due to reclassification was not possible. Additional data regarding a possible trend in the assignment of primary cause of ESRD are available for the 6-year period from 1996 to 2001 (unpublished data, USRDS). During that time, the number of newly registered cases of ESRD with both diabetes and hypertension listed on the Medical Evidence Form (either as primary cause or as comorbid condition) grew 33%, from 34,852 to 46,208. In 1996, when there were 34,852 cases, 91% were attributed to diabetes and in 2001, when there were 46,208 cases, doctors attributed 89% to diabetes. Thus, in patients with both conditions, no shift from a diagnosis of hypertensive ESRD to diabetic ESRD has occurred in recent years.

Does the increasing number of individuals with ESRD due to diabetes result from the rising prevalence of diabetes?

According to the Diabetes Surveillance Program of the CDC, between 1984 and 1996 the population of individuals with diabetes in the United States grew 40% (from 6.1 to 8.5 million), while the increment in the number of persons initiating treatment for ESRD attributed to diabetes was more than 300% (from 6981 to 31,647). If the age-specific incidence rates of ESRD in that population had remained unchanged, the number of persons initiating treatment for ESRD attributed to diabetes would have grown only to 9548 in 1996, an increment of 2576. The actual increment of 24,666 cases (tenfold that attributable to growth of the population at risk) can only mean that the risk of developing ESRD (being accepted to a renal replacement therapy program) increased in patients with diabetes between 1984 and 1996. This is clearly illustrated if the data are presented as the incidence rate of ESRD in the population with diabetes in the United States.

The rising risk of ESRD in patients with diabetes

The incidence rate of ESRD in the population with diabetes is shown in Figure 2 for calendar years 1984 to

![Fig. 1. The number of individuals initiating treatment for end-stage renal disease (ESRD) in the United States, according to cause and calendar year, 1980 to 1999 (RenDER system of the United States Renal Data System (USRDS) (http://www.usrds.org). The vertical line A marks the publication of the clinical trial showing the renoprotective effect of angiotensin-converting enzyme (ACE) inhibition [15]. Abbreviations are: DM, diabetes mellitus; HTN, hypertension; GN, glomerulonephritis.]
1996 according to age and race. Among whites (Fig. 2, left panel), most of the diabetes in the youngest age group (younger than 45 years) can be considered as type 1 and in the older age groups as type 2. Gender-specific rates are shown for the youngest age group because the incidence rate in women was about half that seen in men, but the combined rate is shown for older age groups where the gender-specific rates were similar. In all groups, the incidence rate of ESRD increased over the 13-year time frame. Initially the incidence rates of the three oldest age groups were lower than that in the youngest group, but they increased more steeply and exceeded or matched the rate in the young by 1996. Among blacks, where type 2 diabetes predominates in all age groups, age-specific incidence rates of ESRD (Fig. 2, right panel) were twice those for whites and increased similarly over the 13-year time frame. By 1996, the age-adjusted rates were 590.3 versus 312.1 per 100,000 diabetics per year, for blacks and whites, respectively. Except for the absence of a gender difference in the youngest age group, the age-specific trends paralleled those in whites.

To summarize the secular trends in incidence rates of ESRD in the population with diabetes, the age-specific incidence rates were regressed against calendar year, the slope representing the average annual increment in risk of ESRD (Table 1). Among whites younger than age 45 years, the slopes fit to the gender-specific incidence rates were significant for both women and men ($P = 0.049$ and $P = 0.01$, respectively), and the slope for women was significantly less than for men, 2.8 versus 7.3 cases per
100,000 per year, respectively ($P = 0.03$). Although significant, these slopes pale in comparison with the steeper slopes in the older age groups ($19, 26$, and $15$ cases per 100,000 per year for the age groups $45$ to $64$, $65$ to $74$, and $75+$ years, respectively; $P < 0.0001$). Curiously, the annual increments in the incidence rate of ESRD were significantly higher in the age group $65$ to $74$ years ($P < 0.0001$) than in the age groups $45$ to $64$ or $75+$ years. Among blacks, the trends in age-specific rates were similar and proportionate to those for whites (i.e., about twice as large) (Table 1).

### Table 1. Average annual increment in the incidence rate of end-stage renal disease (ESRD) attributed to diabetes in people with diabetes in the United States population during the period 1984 to 1996, according to age and race

<table>
<thead>
<tr>
<th>Age groups</th>
<th>White</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;45 women</td>
<td>2.8</td>
<td>20.9</td>
</tr>
<tr>
<td>&lt;45 men</td>
<td>7.3</td>
<td>15.9</td>
</tr>
<tr>
<td>45–64</td>
<td>19.2</td>
<td>34.3</td>
</tr>
<tr>
<td>65–74</td>
<td>25.6a</td>
<td>50.1b</td>
</tr>
<tr>
<td>74+</td>
<td>15.4</td>
<td>36.1</td>
</tr>
</tbody>
</table>

$^aP < 0.0001$ in comparison with other age groups; $^bP < 0.006$ in comparison with other age groups.

Has the incidence of ESRD been artificially inflated by increased access to renal replacement therapy or increased acceptance of it by individuals with diabetes?

Renal replacement therapy has been widely available in the United States since the middle 1980s [1], and the cost has been largely covered by the Medicare ESRD program for the last 30 years [2]. However, within certain segments of the population such as the elderly, delays in access or acceptance of renal replacement therapy resulted in an undercounting of the ESRD population [10]. Removal of these barriers and more complete ascertainment of the ESRD population would result in an apparent increase in the incidence rate over time. The white population in the age group $45$ to $64$ years is a segment of the population that would have encountered the fewest reasons for delayed access or acceptance, and the incidence rate of ESRD in this group has increased steadily since 1984 (Fig. 2, left panel). In contrast, the incidence rate of ESRD in blacks in the age group $75+$ years was constant until around 1988 when it began increasing steeply (Fig. 2, right panel). After a few years, the steep increase abated and the continuing increase paralleled the younger age groups. This pattern is consistent with delayed access or acceptance of renal replacement therapy in this segment of the population. Thus, undoubtedly, increasing access or acceptance has contributed to the overall increase in the incidence rate of ESRD in the diabetic population, but these factors are unlikely to have contributed materially to the threefold increase in the incidence rate from $107.0$ to $337.7$ per $100,000$ in the age group $45$ to $64$ years in the white population.

### Risk of ESRD in people with diabetes is increasing despite widening availability of effective interventions

In the early 1980s, Danish authors reported that treatment of hypertension in patients with type 1 diabetes and proteinuria slowed down the loss of renal function [11, 12]. Subsequently the beneficial effect of treatment of hypertension was confirmed in larger studies in patients with type 1 and type 2 diabetes [13, 14], and the use of angiotensin-converting enzyme (ACE) inhibitors was shown specifically to have renoprotective effects [15–20]. Similar effectiveness was demonstrated recently for treatment with angiotensin receptor antagonists [21–23]. All of these demonstrations of effectiveness, however, have been based on short-term follow-up, and the long-term effects of these interventions remain unknown.

Implementation of these interventions in the United States population has a short history. Antihypertensive treatment of patients with diabetes was suggested in the early 1970s [24] but infrequently implemented. According to the 1976 to 1980 NHANES II survey of the population aged 18 years and older, $44\%$ of the individuals with hypertension were treated with antihypertensive agents [25]. Since then, the prevalence of treated hypertension has increased progressively in the diabetic population so that by the time of the NHANES III survey (1988 to 1994), the proportion treated with antihypertensive agents had nearly doubled to $82\%$ [26].

The major classes of antihypertensive drugs in use in the United States population have also changed over the past two decades [27, 28]. In 1982, antihypertensive treatment was recommended only if blood pressure was greater than or equal to $160/95$ mm Hg; and the principal drugs were thiazide diuretics, beta blockers, central adrenergic agonists, and peripheral vasodilators such as hydralazine. Between 1982 and 1993, blood pressure treatment goals were lowered to $140/90$ mm Hg, and use of ACE inhibitors became widespread. After ACE inhibitors were recommended specifically for the prevention of declining renal function in type 1 diabetes in 1993 [15], treatment with ACE inhibitors was instituted in a large proportion ($45\%$) of patients with diabetes [29], and the proportions became even higher if hypertension or microalbuminuria was present ($62\%$ to $80\%$) [30].

Despite the success in implementing antihypertensive treatment in individuals with type 1 or type 2 diabetes and widespread use of ACE inhibition, no tempering of the rising risk of diabetes-related ESRD has yet appeared in any age category in the United States population (Figs. 1 and 2). In striking contrast, the annual increase in the
number of incident cases of ESRD attributed to hypertension has slackened since 1989 (Fig. 1). The reason for the absence of a similar slackening in the annual increase in ESRD attributed to diabetes is unknown.

Has improved treatment of diabetes and hypertension allowed more patients to survive long enough to develop ESRD?

ESRD is a late-appearing complication of diabetes, the risk rising significantly after 10 to 15 years duration of diabetes [31]. If survival of the population with diabetes has been prolonged by better treatment, particularly treatment of cardiovascular disease, the major cause of death in this population, patients with diabetes of such long duration would comprise a growing fraction of the diabetic population. The result would be both a growing prevalence of diabetes and a rising incidence rate of ESRD related to diabetes, not because of changing risk but because of the growing proportion of them at high risk due to long duration diabetes.

Very strong evidence against this hypothesis comes from several sources. First, consider the supposed postponement of cardiovascular mortality in patients with diabetes. The recently reported clinical trial (RENAAL) of the effectiveness of angiotensin II receptor blockade in patients with type 2 diabetes and nephropathy examined both the incidence of ESRD and the mortality rate from cardiovascular disease [21]. By the end of that 4-year trial, the cumulative incidence of ESRD in the treated group was 25%, while it had reached 25% in the placebo group roughly a year earlier. Thus treatment with angiotensin II receptor blockade slowed down the rate of the development of ESRD by 1 year. Surprisingly, this treatment had no effect on the morality rate. Both the morbidity and mortality from cardiovascular causes were similar in the treated and placebo groups. Management of these patients under the carefully controlled conditions of a clinical trial did not extend their duration of diabetes and reduced, rather than increased, the number of ESRD events within the 4-year span of the trial. Therefore, none of the increase in ESRD can be attributed to reduced cardiovascular mortality due to better disease management with interruption of the renin-angiotensin system.

Population data on cardiovascular mortality in patients with diabetes are consistent with the RENAAAL results in finding no evidence for a substantial reduction in cardiovascular disease mortality in people with diabetes during the last 20 years. The National Center for Health Statistics followed two representative samples of the United States population (NHANES I in 1971 to 1975 and NHANES I Epidemiologic Follow-up Survey in 1982 to 1984) for 8 to 9 years. The individuals with diabetes in these samples were mainly patients with type 2 diabetes. Age-adjusted heart disease mortality rate fell only 13% in diabetic men and actually rose 23% in diabetic women, at the same time it was falling by 36% and 27% in nondiabetic men and women, respectively [32]. In the same study, all-cause mortality declined only minimally in people with diabetes. In the absence of a decrease in mortality, it is difficult to justify a claim that better treatment has extended survival and increased the duration of diabetes in the population.

Moreover, the population based study of patients with type 2 diabetes in Rochester, Minnesota, does not support the hypothesis that a secular trend in the proportion of patients with long duration diabetes can account for the increasing risk of ESRD [33]. Data from three decades (1970s, 1980s, and 1990s) were analyzed, and there was no change in the mean duration of type 2 diabetes and no secular increase in the incidence of proteinuria after the diagnosis of diabetes to account for the secular increase in ESRD.

Further evidence, albeit indirect, against any increase in the duration of diabetes in the United States population, comes from a recent report from CDC that assessed change in the prevalence of diabetes (diagnosed and undiagnosed) in the United States population during the last decade by comparing data from NHANES IV (conducted in 1999 and 2000) with data from NHANES III (conducted in 1988 to 1994). Surprisingly, the prevalence of diabetes in the population age 20 years and older changed little over time [34]. In the white population, the age-adjusted prevalence of diabetes was 7.4% in both surveys, while it increased from 12.3% to 14.9% in blacks (Fig. 3). Any increase in the average duration of diabetes in the population would increase the population size. Therefore, a stable prevalence of diabetes in the adult white population does not support a hypothesis that the proportion of patients with long duration diabetes is increasing in the
United States population. Furthermore, the rising prevalence of diagnosed diabetes and decreasing prevalence of undiagnosed diabetes in the black population implies that a large number of newly diagnosed patients were added to the population, reducing the proportion of the black population with long duration diabetes.

**DISCUSSION**

**The epidemic of ESRD in the population with diabetes is real**

The aggregate data sources used in this review provide an opportunity to examine time trends in a situation where individual data are not available. Unfortunately, this type of study design is subject to a number of limitations that readers must take into account when interpreting the findings. One factor that may have contributed substantially to the growth of the ESRD population was improved ascertainment by USRDS of ESRD over time. Moreover, since only patients who accept treatment are registered with USRDS, increasing acceptance of renal replacement therapy among diabetic patients may also have accelerated growth of the number of cases. Evidence to support a concern that problems of ascertainment or acceptance did affect the trends is seen in the eldest age group in the black population (Fig. 2). There was a lag of almost a decade before the incidence rate in that group began to increase in parallel with other age groups. However, evidence that these factors cannot account for more than a fraction of the increased number of registered new cases of ESRD each year is seen in the steady increase in the incidence rate of ESRD attributed to diabetes in the age group 45 to 64 years in the white population (Fig. 2). In this working-age segment of the population, which would be motivated to seek renal replacement therapy and would encounter few of the barriers that might deter individuals of similar age in a minority population, the incidence rate of 107.0 per 100,000 individuals with diabetes in 1984 had doubled to 216.6 per 100,000 in 1990 and tripled to 337.7 per 100,000 by 1996. It is not plausible that ascertainment and acceptance of renal replacement therapy tripled in this population segment since 1984.

Other potential pitfalls of this study design that might explain some of the rising incidence of ESRD in the population with diabetes include changing preferences for therapy tripled in this working-age segment of the population, which would be motivated to seek renal replacement therapy and would encounter few of the barriers that might deter individuals of similar age in a minority population, the incidence rate of 107.0 per 100,000 individuals with diabetes in 1984 had doubled to 216.6 per 100,000 in 1990 and tripled to 337.7 per 100,000 by 1996. It is not plausible that ascertainment and acceptance of renal replacement therapy tripled in this population segment since 1984.

The second area of research is an epidemiologic inquiry into risk factors and risk indicators for the prevention of ESRD in diabetes.

**Implications for future research on etiology and prevention of ESRD in diabetes**

Several areas of research require urgent attention. One high priority area for research is the natural history of renal function loss in individuals with diabetes. Herefore, research has focused on the continuing loss that occurs after impaired renal function has become established, which we can consider “advanced renal function loss.” Earlier in the process, opportunities for effective intervention may become evident through knowledge of the natural history of “early renal function loss.” Furthermore, the concept that proteinuria plays an essential role in the process must be re-examined. The risk of ESRD has increased without any clear evidence for an increasing risk of proteinuria in the population with diabetes. Therefore, either the probability of progressing to ESRD in patients with diabetes and proteinuria has increased or declining renal function occurs in patients with diabetes before proteinuria develops. Thus, prospective studies are needed to examine renal function decline in individuals with diabetes and normoalbuminuria or microalbuminuria.

The second area of research is an epidemiologic inquiry into risk factors and risk indicators for the
development of ESRD in diabetes that have increased over time and could account for the observed epidemic. Given the goal of identifying determinants of early renal function decline, particular attention should be paid to characteristics of patients with diabetes before nephropathy has developed (such as the use of prescription or nonprescription medications) and should include the antecedents of diabetes itself (such as obesity in the case of type 2 diabetes).

A secular increase in obesity, the most important risk factor for type 2 diabetes, has been amply documented. Both absolute body weight and the prevalence of obesity have increased in the United States population in recent decades [38, 39]. Furthermore, the population with diabetes has shared in the general trend of increasing obesity. In 1970 to 1974, 33% of the patients with newly diagnosed type 2 diabetes in Rochester, Minnesota, were obese as compared to 49% in 1985 to 1989 [40]. The evidence linking obesity as a risk factor for ESRD is tenuous, and more research needs to be done. Similarly, other antecedents of glucose intolerance need to be examined for their possible effects on renal function loss at the same time that they are predisposing to diabetes.

Regarding secular changes in the treatment of persons with diabetes, one example has already been discussed, the increasing proportion treated with antihypertensive agents and ACE inhibitors. An argument against considering them as contributors to the rising risk of ESRD is the fact that patients with hypertension have also experienced a similar secular increase in treatment with these agents but the occurrence of ESRD attributed to hypertension leveled off in the 1990s and did not increase in parallel with diabetes-related ESRD (Fig. 1).

Other prescription medicines ought to be considered as well. Individuals with diabetes are 1.7 to 2.1 times more likely to receive prescription medicines than nondiabetics, even after excluding antidiabetic medications [41]. The pharmacologic properties of some commonly used medications are modified in the presence of diabetes [42], but the consequences for the kidneys have not been studied. An exception is the potential nephrotoxicity of over-the-counter analgesics such as acetaminophen and nonsteroidal anti-inflammatory medicines, which have been examined in case control studies. While the Physician’s Health Study of a cohort of nondiabetic men did not detect any association between analgesic use and moderate renal insufficiency [43], a population-based study in Sweden found an increased risk of chronic renal insufficiency associated with use of acetaminophen or aspirin in people with diabetes [44].

### Implications for patient care

The increasing risk of ESRD in diabetes, if unabated, will increase enormously the number of new cases of ESRD in the United States population during the next 10 years (Table 2). The number of individuals with newly diagnosed ESRD due to diabetes in the year 2000 was 41,772 and by the year 2010 this number is predicted to reach 69,136 individuals, an increase of 65.5%. The total number of individuals on renal replacement therapy with ESRD due to diabetes in 2000, new cases plus the carryover from previous years, was 131,173, and the number is predicted to be 233,884 in 2010, a 78.3% increase.

The increase in prevalence of patients with diabetes-related ESRD in the United States will place a disproportionate burden on the ESRD health care delivery system. In addition to the resources usually required for renal replacement therapy, ESRD patients with diabetes require specialized resources to maintain their glycemic control and treat diabetes-related complications, such as diabetic retinopathy, peripheral vascular disease, and coronary artery disease. Moreover, the age group 75+ years will experience the largest relative increases. The more comprehensive care needed by these patients will require additional staff: diabetes specialists and nurses as well as nephrologists and technicians, providers who are already in short supply. Furthermore, the unique needs of the diabetic population must be incorporated into the training programs for all the staff. Planning for the projected growth in requirements for resources, which will occur in the near future, requires urgent attention.

### ACKNOWLEDGMENTS

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### Table 2. Number of new onset and prevalent cases with diabetes-related end-stage renal disease (ESRD) in the United States population observed in 2000 and predicted for 2010

<table>
<thead>
<tr>
<th>Age groups years</th>
<th>Observed in 2000</th>
<th>Estimated in 2010</th>
</tr>
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<tbody>
<tr>
<td>New onset cases</td>
<td></td>
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<tr>
<td>&lt;45 years</td>
<td>4106</td>
<td>4448</td>
</tr>
<tr>
<td>45–64</td>
<td>17,834</td>
<td>26,420</td>
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<tr>
<td>65–74</td>
<td>12,167</td>
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</tr>
<tr>
<td>75+</td>
<td>7665</td>
<td>19,172</td>
</tr>
<tr>
<td>Total</td>
<td>41,772</td>
<td>69,136</td>
</tr>
<tr>
<td>Prevalent cases</td>
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<td></td>
</tr>
<tr>
<td>&lt;45 years</td>
<td>17,742</td>
<td>18,329</td>
</tr>
<tr>
<td>45–64</td>
<td>60,224</td>
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