Clinical Diagnoses Before Age 75 and Men’s Survival to Their 85th Birthday: The Manitoba Follow-up Study

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Purpose: Of all Canadian and American men who live to age 75 years, about half can expect to live to age 85. Our objective is to examine how clinical diagnoses made before age 75 relate to a man’s survival to age 85 years. Design and Methods: Since 1948, a cohort of 3,983 young men (mean age of 31 years at entry) has been followed with routine contact and medical examinations to prospectively document incident disease. Over 62 years of follow-up, 2,414 of the cohort lived to celebrate their 75th birthday. Of these survivors, 1,060 (44%) died before their 85th birthday. Cox proportional hazard models were used to examine the effects of ischemic heart disease, cancer, cerebrovascular disease, diabetes mellitus, peripheral arterial disease, and chronic obstructive pulmonary disease on all-cause mortality between age 75 and 85 years. Results: Modeled as six binary risk factors at age 75 years, all were significantly ($p < .01$) and independently related to 10-year mortality. Multivariate risk ratios ranged from 1.36 to 1.46 except for chronic obstructive pulmonary disease with a risk ratio of 1.85 (95% CI: 1.38, 2.49). The cumulative 10-year probability of survival from age 75 to 85 among men with none of these diagnoses was 63%, 52% for any one diagnosis, 39% for two diagnoses, and 22% for three or more diagnoses. Implications: Joint independence of these six common clinical diagnoses implies that each is important and their effects on mortality are cumulative.

Key Words: Chronic disease, Men, Mortality, Prospective study

It is acknowledged that in many parts of the world, individuals are living longer and healthier lives (World Health Organization, 2008). In the United States and Canada, for instance, males at birth now have a life expectancy of 76 and 78.3 years, respectively (World Health Organization, 2010). Indeed, the life expectancy of a 75-year-old American or Canadian man now exceeds 85 years. This “oldest old” age category (those more than 85 years) is the fastest growing segment of the population in most industrialized countries (Christensen, Dobramysl, Rauch, & Vaupel, 2009; National Center for Health Statistics, 2011; Statistics Canada, 2006; Suzman & Riley, 1985). Nevertheless, cardiovascular disease, cancer, chronic lower respiratory disease, cerebrovascular disease, and diabetes continue to take their toll as the five leading causes of death among men 75–84 years of age in the United States and Canada (Centers for Disease Control and Prevention, 2010; Statistics Canada, 2011). Numerous lifestyle factors as well as diseases and conditions detected earlier in life have been identified in relation to subsequent mortality, specifically to mortality in late life. Of particular interest are those conditions listed above, notably...
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acute events such as ischemic heart disease or stroke, chronic conditions such as diabetes mellitus or peripheral arterial disease, and adverse lifestyle factors such as smoking, excessive alcohol consumption, and lack of physical activity (Ljungquist, Berg, & Steen, 1995; Menotti, Mulder, Nissinen, Feskens, et al., 2001; Newman et al., 2009; Stamler et al., 1999; Terry et al., 2005; Tice et al., 2006; Willcox et al., 2006; Yates, Djousse, Kurth, Buring, & Gaziano, 2008). Some investigators have reported on the comorbidity of these diseases and on their combined effects on mortality. In the Physicians’ Health Study, potentially modifiable risk factors were related to 20-year survival of older men, assessing the probability of survival with increasing number of adverse factors at baseline (Yates et al., 2008). Another study has examined predictors of survival at ages 75, 80, 85, and 90 years, relating number of risk factors at baseline and probability of survival and exceptional survival at those ages (Willcox et al., 2006). Lee and colleagues devised a prognostic index incorporating self-reported behavioral and comorbidity variables, including disease and functional status to predict 4-year mortality in older adults (Lee, Lindquist, Segal, & Covinsky, 2006). Others have looked at the comorbidity of five major conditions, some mentioned earlier—coronary artery disease, cerebrovascular disease, cancer, diabetes, and hypertension—among older individuals and their impact on mortality (Fillenbaum, Peper, Cohen, Cornoni-Huntley, & Guralnik, 2000). The Cardiovascular Health Study (CHS), with an initial cohort aged 65 years and older, investigated the predictive nature of baseline characteristics on 5-year and 16-year survival (Fried et al., 1998; Newman et al., 2009).

Reports such as these have generally examined medical conditions and risk factors diagnosed, often self-reported, at a single point in time with a variable follow-up period to death. With continued calls for life course approaches to chronic disease epidemiology, examining longer term history of chronic disease development and subsequent mortality might prove beneficial in obtaining a better understanding of survival among the oldest old (Ben-Shlomo & Kuh, 2002). Numerous diseases, many relatively common and modifiable, have been found to be related to mortality. However, a thorough examination of their impact, alone or in combination, on mortality throughout a 10-year period of time in an older man’s life has yet to be reported.

The purpose of this paper was to examine clinical diseases diagnosed in men by age 75 years in relation to death by age 85 years. Our analysis used prospectively collected clinical data from the all-male cohort of the Manitoba Follow-up Study (MFUS) and focused solely on those men who lived to at least their 75th birthday. Our general objectives were to determine the prevalence of six clinical diagnoses (ischemic heart disease, cerebrovascular disease, cancer, diabetes mellitus, peripheral arterial disease, and chronic obstructive pulmonary disease) in men at age 75 years; to compute and compare the 10-year survival rates for men with and without each clinical diagnosis, considering the time since diagnosis prior to age 75 years; and to examine the independent and synergistic effect of multiple clinical diagnoses and determine the incremental risk of mortality in terms of the number of diagnoses.

These objectives led to the following testable null hypotheses:

Hypothesis 1: Each disease diagnosis at age 75 is not related to an increased risk of mortality by age 85 years.

Hypothesis 2: The time prior to age 75 years since diagnosis of each disease is not related to risk of mortality by age 85 years.

Hypothesis 3: The significant disease diagnoses at age 75 (identified in Hypothesis 1) are independent of each other in their effect on risk of mortality by age 85 years.

Hypothesis 4: The number of disease diagnoses at age 75, ranging from zero to six, is not related to an increased risk of mortality by age 85 years.

The six clinical diagnoses we selected not only represent the major causes of death in the age group of interest but unlike other diseases such as congestive heart failure, arthritis, renal disease, and neurological disorders occur with much higher prevalence in our cohort at age 75 years. We adopted the guiding framework that chronic disease diagnoses earlier in life, and the duration of time since diagnoses, may shed light on the rate of survival in older adult males (Ben-Shlomo & Kuh, 2002). In this work, we will examine how six disease diagnoses determined prospectively by age 75 years in men may be relevant in determining differential risk of mortality over the next 10 years to age 85 years.

Methods

The MFUS was established at the University of Manitoba on July 1, 1948, with a cohort of 3,983
men (Mathewson, Manfreda, Tate, & Cuddy, 1987). These men were primarily young recruits in the Royal Canadian Air Force, who during the early years of World War II had attended initial training centres across Canada and were found physically fit. Not all MFUS members became aircrew (e.g., pilots, navigators, observers, gunners), some served as ground crew (e.g., aircraft mechanics, maintenance technicians, air traffic control). A small portion of the cohort was older than the recruits, having served in the military at the beginning of the War or employed at the time by the Ministry of Transport. The mean age of the cohort at entry was 30.8 years, with about 90% between age 20 and 39 years. After the War, the study participants returned to residences throughout Canada, with about 10% relocating to the United States or overseas. Regardless of country of residence throughout their lives, all 3,983 original men remained members of this study. Over time, they assumed a wide variety of occupations, with about a quarter remaining as career pilots. MFUS continues to the present, now in its 64th year of uninterrupted study.

The MFUS protocol required that each study member be examined on a regular basis by his physician, with examinations initially at five-year intervals, and since 1963 every 3 years (Mathewson et al., 1987). Physical examinations included a general health assessment, measurement of blood pressure and body weight, recording of an electrocardiogram, and diagnosis of clinical disease. Consequently, prospective data collection has supported the documentation of physician-diagnosed incident disease, with date and age of first diagnosis. Since 1979, an annual medical contact questionnaire has been sent to each study member, asking him if he had been to see his physician or been hospitalized in the past year, with a signature request authorizing release of information to the study. This questionnaire served the purpose both of maintaining contact with the man and updating his medical information in a more timely fashion between routine medical examination requests. This questionnaire supplements our request for routine medical examination. The clinical information in our database is based only on reports from a physician or hospital and not on self-report from the study member. Although requests for routine medical examinations were discontinued in 2000, the annual contact questionnaire had continued, so documentation of new disease diagnoses continue to be updated in our clinical data files.

A remarkable feature of MFUS has been its ability to maintain contact with all study members, with a very low attrition rate over the 63 years. Our records showed that after 60 years of follow-up to July 1, 2008, there were only 61 men (less than 2% of the original 3,983) whose vital status was unknown, another 3,173 had a documented date of death, and 749 were confirmed alive via contact with the study since July 1, 2008. The date and cause of death of a study member are entered into our database as this information becomes known to us. Often a physician or family member of a study member will notify us of a study member’s passing. We request signed consent from next of kin or an executor to release information to us and then contact the hospital or physician to obtain the exact date and cause of death. At 2008, the mean age of the surviving cohort was 87 years. These features of scope and longevity position MFUS with few other studies of health and aging in the world.

Six clinical diagnoses prior to age 75 years were examined in relation to all-cause mortality between age 75 and 85 years. The diagnoses are defined in the MFUS clinical coding system as:

- Ischemic heart disease—physician diagnosis of myocardial infarction, classical angina pectoris, or acute coronary insufficiency.
- Cerebrovascular disease—definite, suspected or physician-reported stroke or transient ischemic attack.
- Cancer—physician-diagnosed malignancy at any site or in any body system, with the exception of nonmelanoma skin cancer.
- Diabetes mellitus—reported by a physician, with or without submitted biochemical evidence of elevated fasting blood sugar.
- Peripheral arterial disease—definite atherosclerosis of vessels to the legs, with or without claudication, or other diseases of the peripheral arteries.
- Chronic obstructive pulmonary disease—physician-diagnosed respiratory disease of emphysema and chronic bronchitis.

The date of each diagnosis was classified relative to each man’s 75th birthday: at least 20 years prior (before age 55 years), 10–20 years prior (age 55–65 years), or within the past 10 years (age 65–75 years). Neither clinical diagnoses made after a man’s 75th birthday nor clinical diagnoses for any man who died before age 75 years are pertinent to this analysis.
For this analysis, treated hypertension, defined by a reported receipt of prescription for antihypertensive medication or diuretic, and obesity, defined as the date of the third occasion on which a measured body weight resulted in a body mass index exceeding 30.0 kg/m², were noted as potential confounding variables for the relationship between clinical diagnoses and mortality. Smoking was not included as a potential confounding variable in this analysis. Close to three quarters of our entire cohort reported smoking at some time during their lives, but very few of the men surviving to age 75 years were still current smokers. Hence, categories of smoking status at age 75 years such as “ever smoker versus never smoker” or “current smoker versus ex-smoker versus never smoker” would likely not distinguish much variability in mortality between age 75 and 85 years.

The Cox proportional hazard model was used to assess the effect of disease diagnoses on time to death from age 75 to age 85 years. The “event” for every Cox model we present is death between age 75 and 85 years. Men who did not die between age 75 and 85 years are termed “censored” observations. There are four considerations to determine “time to event” and the “censoring status” for each man in our study:

- He died between age 75 and 85 years. His outcome is “age at death -75,” and he is considered an observed event.
- He is alive but not yet age 85 by July 1, 2008. His outcome is “age at July 1, 2008, -75,” and he is considered a censored observation.
- He is alive and older than age 85 on July 1, 2008. His outcome is “10 years,” and he is considered a censored observation.
- He died after age 85 years. His outcome is “10 years,” and he is considered a censored observation.

The range of values during our study for “year at age 75” spans 40 years, from 1964 to 2004, with a median of 1992, and a very narrow interquartile range of 1988 to 1996. During this time, mortality rates of men in Western societies have been declining (Statistics Canada and Canadian Institute for Health Information, 2001). Hence, year at age 75 was included as a continuous variable in every model to control for possible, but nonmeasurable, linear temporal effects of calendar time on mortality. Indicator variables for obesity and treated hypertension were included in all models to control for potential confounding of these factors with the relationship between disease diagnoses and mortality. The effect of each diagnosis was expressed as a relative risk of mortality over the 10-year period. A relative risk of 1.5 for example implies that men with the diagnosis at age 75 are dying over the next 10 years at a rate of death 50% greater than those men without the diagnosis at age 75. The proportionality assumption of the Cox model for each disease diagnosis was assessed with a chi square test with 1 degree of freedom (df) for the difference in -2logL between two models, one with and one without a time-under-study interaction term with a binary indicator for each variable (Allison, 2010).

For Hypothesis 1, the presence or absence of each disease diagnosis before age 75 was modeled as a binary variable in a series of six Cox models.

Two approaches were used to test Hypothesis 2. In the first approach, for each of the six disease diagnoses, we modeled a set of three binary variables: at least 20 years prior (before age 55 years), 10–20 years prior (age 55–65 years), or within the past 10 years (age 65–75 years), relative to no diagnosis of each disease by age 75 years. Our second approach to test Hypothesis 2 was to generate three Kaplan–Meier curves for survival from age 75 to 85 years, stratified as above by age at diagnosis prior to 75 years. These three survival curves were then compared across the age strata at diagnosis with the log-rank chi square test with 2 df, to test whether survival between age 75 and 85 years differed by age at diagnosis for each disease.

Hypothesis 3 was examined via a full multivariate model with all six clinical diagnoses. A backward elimination of variables at the p < .05 level of significance was used. The synergistic effects of these diagnoses were examined by testing all 15 possible interactions between all pairs of the six variables. The likelihood ratio test was used by comparing two models, one with and one without the (product term) variable indicating presence of both diseases in the larger model. The population attributable risk (=prevalence [relative risk – 1]/[1 + prevalence (relative risk – 1)]) was calculated for the final multivariate model to determine the relative importance of each of the six diseases.

Hypothesis 4 was tested in a Cox model by the significance of a categorical variable identifying the number of diagnoses at age 75 years, as one, two, or three to six, relative to none of the six diagnoses. Further, Kaplan-Meier curves were produced for categories of the number of clinical diagnoses at age 75 years.
All statistical analyses were undertaken with SAS version 9.2 software (SAS Institute, Cary, NC). MFUS receives annual approval from the Health Research Ethics Board of the University of Manitoba for ongoing activity, including data analysis.

Results

In 1948, the youngest man in the MFUS cohort was 18 years of age. Thus, all men in this study had the potential to live beyond age 75 years during the course of follow-up to 2010. Over 62 years of follow-up, 2,414 men were known to live to celebrate their 75th birthday. A feature of this study has been the low frequency of men lost to follow-up. Of the 1,569 who were not included in this analysis, 1,549 are known to have died before age 75, and only 20 were lost before their 75th birthday, and hence their vital status remains unknown.

Among the 2,414 study members confirmed alive on their 75th birthday, 1,063 (44%) died before their 85th birthday (follow-up time defined as time from age 75 years to death). By the end of the follow-up period, 1,301 (54%) had lived beyond their 85th birthday (10 years of follow-up censored at age 85 years). Only 50 men (2% of these 2,414) were alive but still younger than 85 years of age at the time of last contact and hence censored with less than 10 years of follow-up time prior to age 85 years.

As shown in Table 1, the prevalence of the six clinical diagnoses at age 75 ranged from 3% (chronic obstructive pulmonary disease) to 21% (ischemic heart disease). The mean age at diagnosis for the six diseases ranged from 63 to 67 years. With the exception of ischemic heart disease at 19% and diabetes mellitus at 15%, the prevalence of long-standing disease more than 20 years prior to age 75 years was only 6%–8%.

Presence of each of the six diagnoses was significantly associated with an increased risk of death between age 75 and 85 years (Table 2). The

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Prevalence at age 75 years, n (%)</th>
<th>Age at diagnosis, mean ± SD</th>
<th>Time from diagnosis to age 75 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;10 years (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Between 10 and 20 years (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;20 years (%)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>510 (21.1)</td>
<td>62.9 ± 8.5</td>
<td>48</td>
</tr>
<tr>
<td>Cancer (any site)</td>
<td>302 (12.5)</td>
<td>67.0 ± 9.2</td>
<td>72</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>239 (9.9)</td>
<td>63.2 ± 8.4</td>
<td>50</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>226 (9.4)</td>
<td>67.0 ± 7.2</td>
<td>67</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>178 (7.4)</td>
<td>66.0 ± 7.4</td>
<td>63</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>71 (2.9)</td>
<td>66.7 ± 6.8</td>
<td>66</td>
</tr>
</tbody>
</table>

Table 2. Relative Risk With 95% Confidence Intervals for Mortality by Age 85 Years From 12 Cox Proportional Hazard Models of Clinical Diagnoses Before Age 75 Years

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>Diagnosed before age 75 years</th>
<th>&lt;10 years</th>
<th>Between 10 and 20 years</th>
<th>&gt;20 years</th>
<th>Log rank test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>1.43 (1.25, 1.64)</td>
<td>1.22 (1.00, 1.47)</td>
<td>1.51 (1.22, 1.88)</td>
<td>1.94 (1.51, 2.50)</td>
<td>.006</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1.65 (1.35, 2.01)</td>
<td>1.56 (1.22, 2.00)</td>
<td>1.76 (1.25, 2.48)</td>
<td>2.09 (1.04, 4.20)</td>
<td>.901</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.55 (1.29, 1.86)</td>
<td>1.43 (1.14, 1.78)</td>
<td>1.60 (1.14, 2.26)</td>
<td>3.62 (2.04, 6.40)</td>
<td>.009</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.99 (1.48, 2.66)</td>
<td>2.12 (1.50, 3.00)</td>
<td>1.41 (0.76, 2.63)</td>
<td>3.88 (1.45, 10.4)</td>
<td>.323</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.45 (1.20, 1.74)</td>
<td>1.39 (1.08, 1.79)</td>
<td>1.49 (1.12, 1.99)</td>
<td>1.53 (1.00, 2.34)</td>
<td>.962</td>
</tr>
<tr>
<td>Cancer (any site)</td>
<td>1.36 (1.15, 1.61)</td>
<td>1.43 (1.18, 1.74)</td>
<td>1.24 (0.86, 1.78)</td>
<td>1.10 (0.61, 2.00)</td>
<td>.641</td>
</tr>
</tbody>
</table>

Note: Twelve models are represented in this table, six models each with one binary indicator for presence or absence of each clinical diagnosis at age 75 and six models with three indicators defining categories of time since diagnosis. The reference category for all relative risk estimates is no clinical diagnosis. Each model contains three other variables: year at age 75 as a continuous variable to control for temporal effects of mortality and two indicator variables to control for potential confounding of obesity and treated hypertension prior to age 75 years. The log rank statistic tests for differences in survival across the three strata of time since diagnosis.

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test for the proportionality assumption of the Cox model showed that the relative hazard of death was constant for each disease, that is, the hazard functions for those with and without the diagnosis remained proportional to each other at all points in time between age 75 and 85 years. Twelve models are represented in Table 2, six models each with one binary indicator for presence or absence of each clinical diagnosis at age 75 and six models with three indicators defining categories of time since diagnosis. The reference category for all relative risk estimates is no clinical diagnosis. Each model also contains three other variables: year at age 75 as a continuous variable to control for temporal effects of mortality, and two indicator variables to control for potential confounding of obesity and treated hypertension prior to age 75 years.

Overall, a diagnosis of ischemic heart disease by age 75 years brought a 1.43 (95% CI: 1.25, 1.61) times greater risk of death by age 85. Those men diagnosed before age 55 years and still alive at age 75 had almost twice the risk of death during the next 10 years (1.94 [95% CI: 1.51, 2.50]). This was in contrast to a 51% increased risk of death if ischemic heart disease was first diagnosed between 65 and 75 years, relative to men free of ischemic heart disease. The three survival curves for men diagnosed with ischemic heart disease before age 55 years, between age 55 and 65 years, and between age 65 and 75 years of age were significantly different (log-rank test \( p = .006 \)). A similar and significant difference in mortality is apparent for men stratified by time since previous cerebrovascular disease (log-rank test \( p = .009 \)). Diagnosis of the other four diseases brought an increased risk of death after age 75, regardless of time since diagnosis. Of note, is that the effect on mortality of a cancer diagnosis known at age 75 diminishes with increasing length of time since diagnosis. Perhaps those diagnosed with cancer earlier in life (before age 65 years) and alive at age 75 years may be in remission, and their risk of death between age 75 and 88 years is not significantly different from men who have remained cancer free to age 75 years.

An important observation is that all six diseases examined had independent effects on mortality and each was significantly associated with an increased risk of mortality (Table 3). The omnibus chi-square test for the joint effect of 15 possible interaction terms in the full model (fit of model with 24 variables minus fit of model with 9 variables) was nonsignificant, \( \chi^2 = 16.27 \), with 15 df, \( p > .25 \). The interaction term between chronic obstructive pulmonary disease and peripheral arterial disease was significant at \( p = .02 \) and all other 14 two-factor interaction terms in the full multivariate model were nonsignificant at \( p > .10 \). Five of the six clinical diagnoses had relative hazards ranging from 1.36 to 1.46, a very narrow range of effect, with the relative risk for chronic obstructive pulmonary disease being greatest (1.85 [95% CI: 1.38, 2.49]). With the relative risk of mortality being similar for most disease diagnoses, it is relevant to consider the prevalence of the diagnosis to interpret its impact at the population level on mortality. The attributable risk for each diagnosis shown in Table 3 suggests that for all other diagnoses, ischemic heart disease accounts for 7% of the mortality by age 85 years, followed by cancer with 4%.

The independence of effects of these significant factors and the fairly consistent magnitude of effects among them suggests that the number of diseases present at age 75 years might be as important as the actual combination of diseases diagnosed. This was explored in a further model (Table 4 and Figure 1), where the number of clinical diagnoses—any one, any two, or three or more—were modeled relative to the 54% of men at age 75 years who

Table 3. Multivariate Relative Risk of Mortality Between Ages 75 and 85 Years for Clinical Diagnoses Before Age 75 Years Among 2,414 Men

<table>
<thead>
<tr>
<th>Disease diagnosis</th>
<th>Relative risk (95% confidence interval)</th>
<th>Population attributable risk (%)</th>
<th>Kaplan–Meier cumulative probability of survival to age 85 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>1.36 (1.18, 1.57)</td>
<td>7.0</td>
<td>0.45</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1.46 (1.20, 1.79)</td>
<td>3.3</td>
<td>0.38</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1.37 (1.14, 1.66)</td>
<td>3.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1.85 (1.38, 2.49)</td>
<td>2.4</td>
<td>0.33</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.36 (1.13, 1.64)</td>
<td>3.4</td>
<td>0.43</td>
</tr>
<tr>
<td>Cancer (any site)</td>
<td>1.36 (1.15, 1.62)</td>
<td>4.3</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Note: This multivariate model also contains three other variables: year at age 75 as a continuous variable to control for temporal effects of mortality and two indicator variables to control for potential confounding of obesity and treated hypertension prior to age 75 years.
were free of all six clinical diagnoses. Having a single diagnosis (any one of the six) was associated with a 40% increased risk of mortality relative to the man with none of these six diseases at age 75 years. A man with two, or three or more diagnoses had a 1.95 and 2.97 times greater risk of mortality compared with the man free of all six disease diagnoses, respectively. There was a clear separation of risk of mortality, as shown in Figure 1, with increasing number of diagnoses. The cumulative probability of survival from age 75 to 85 years among men with none of these diagnoses was 63%, 52% for any one disease, and down to 22% if they had three or more clinical diagnoses by age 75 years.

Discussion

The MFUS cohort has been followed with routine medical examinations to document physician-diagnosed disease and associated conditions since 1948. The youngest man at entry to the study had the potential to be followed to his 75th birthday. Indeed, 60% of the cohort celebrated a 75th birthday, but of these, almost half (44%) died before their 85th birthday. Six commonly diagnosed diseases were examined in our analysis. Many of the survivors (41%) had none of these diseases and another 34% had only one present by age 75 years. Thus, one quarter of our study members alive at age 75 years were living with two or more of the diseases studied. The results of this study have important implications regarding disease diagnoses that will separate those 75-year-old men who will survive from those who will not survive the next 10 years. The effects of the six diseases on mortality are independent of one another, and hence, their effects are multiplicative. The magnitude of effect of five of the six disease diagnoses is relatively similar.

Several other studies have examined the joint and independent effects of groups of baseline risk factors and disease conditions on mortality in later life but without incorporating time from disease diagnosis. As with our results, others generally found that as numbers of risk factors or disease conditions at baseline increased, the probability of survival to an advanced age decreased. The FINE (Finland, Italy, Netherlands, Elderly) Study, with 2,285 men 65–84 years old, pooled chronic diseases into six groups: coronary heart disease, heart failure, cerebrovascular accidents, intermittent claudication, chronic obstructive pulmonary disease, diabetes, and cancer (Menotti, Mulder, Nissinen, Giampaoli, et al., 2001). They found increasing risk of 10-year mortality with increasing numbers of diseases at baseline; results for Finland compared closely with our results, with hazard ratios of 1.36, 2.62, and 3.11 for one, two, and three or more diseases, respectively. The Healthy Ageing Longitudinal Study in Europe, combining cohorts from the FINE and SENeca (Survey in Europe on Nutrition and the Elderly: a Concerted Action) studies, also found increasing risks of all-cause and cause-specific mortality with fewer healthy risk factors (Knoops et al., 2004). Fillenbaum and colleagues found that history of coronary artery disease, cerebrovascular disease, diabetes, and cancer significantly increased the risk of six-year mortality among older persons and comorbidity of those conditions increased the risk even further (Fillenbaum et al., 2000). In relating potentially modifiable risk factors to 20-year survival of older men (mean age 72 years), the Physicians’ Health Study found that the probability of survival to 90 years decreased
from 54% with no adverse factors to 14% with three factors and only 4% with five factors (Yates et al., 2008). The Honolulu Heart Program/Honolulu Asia Aging Study observed that the probability of a 55-year-old man with no risk factors at baseline surviving to age 85 was 0.69, but only 0.22 for a man with six or more baseline risk factors (Willcox et al., 2006). Using a wave of the Health and Retirement Study, Lee and colleagues developed an index predicting 4-year mortality among older persons using 12 independent factors including the six comorbid conditions of diabetes, cancer, lung disease, heart failure, smoking, and body mass index (Lee et al., 2006). The CHS reported 20 significant predictors of 5-year mortality among a cohort aged 65 years and older, including high levels of systolic blood pressure and fasting blood glucose, whereas increased body weight appeared to have a protective effect (Fried et al., 1998). In their subsequent analysis of 16-year mortality, CHS investigators found similar results to their 5-year analysis, albeit with attenuated hazard ratios (Newman et al., 2009). A limitation acknowledged by CHS investigators was their assessment of risk factors and conditions at a single point in time.

Although much understanding of the effects of chronic diseases in the older adult has been published, our findings with the MFUS cohort contribute to this discussion. We confirmed an independent effect on mortality of six disease diagnoses. We examined the effect of time from diagnosis to age 75 years and reported gradients of increasing risk for diseases of cerebrovascular disease and ischemic heart disease with longer durations since diagnoses. Further, our results are based on analyses of data from a large cohort of men, with information on both prospectively diagnosed disease and documented mortality.

We focused on all cancers, chronic obstructive pulmonary disease and vascular disease, including cardiovascular, cerebrovascular and peripheral vascular disease, as well as diabetes mellitus. By age 75, more than 1 in 5 men had been diagnosed and survived cardiovascular disease, 1 in 8 was living with a cancer diagnosis, and 1 in 10 with another vascular disease.

Among the strengths of our study, perhaps the most notable has been our ability to prospectively document physician-diagnosed disease over a long period of time and over ages of increasing disease incidence. This study design has permitted the assessment of effects of clinical diagnoses on mortality without risk of recall bias, which is inherent in self-reported data. As well, the narrow age range at entry to the study has minimized period and cohort effects, as most study members passed through the 75- to 85-year window during a relatively short calendar period. In addition, the homogeneity of our cohort at entry, almost exclusively Caucasian men free of heart disease, essentially eliminated some sources of potential confounding.

A potential limitation in our study comes from the recognition that there was a more selective recruitment process for aircrew for the Air Force, compared with both of the other branches of the Armed Forces, and compared with men not recruited for World War II. This may have resulted in healthier, or in some ways, more elite subjects in this cohort than may be found in the general population. If indeed MFUS members were healthier at the beginning of the study and in higher social positions than the general population, then the potentially confounding effects of socioeconomic characteristics may have been controlled as a result of this more homogeneous cohort composition. Our “men only” study can be viewed not only as a limitation in regard to the generalizability of our results but also as a strength in terms of having a large homogeneous sample from which to draw inferences. One might consider the selection of the six specific clinical diagnoses over other diagnoses such as arthritis, renal disease, and neurological conditions as a limitation. However, we did so primarily because of the higher incidence of the six at younger ages, thereby selecting chronic diseases with higher prevalence in 75-year-old men.

In the United States and Canada today, 12%–14% of the population is 65 years or older. These percentages are projected to rise to about 20% by 2030 in the United States and close to 25% by 2036 in Canada (He, Sengupta, Velkoff, & DeBarros, 2005; Statistics Canada, 2010). Today, it is expected that more than half of all American and Canadian men will reach age 75 years. We analyzed the 10-year mortality experience, with almost complete follow-up of 2,414 75-year-old men and found that almost half of these men (44%) will die before age 85 years.

In practice, our message is not that 75-year-old men visit their physicians to discuss their short-term prognoses. Instead, it is hoped that men much younger, in conversation with their physicians, understand the impact of the diseases we studied. Acute events of cerebrovascular and ischemic heart disease diagnosed earlier in life will reduce their likelihoods of survival after age 75 years. Alone or
in combination with other chronic disease diagnoses, each will play an important role in assessing the likelihood for their survival to their 85th birthdays. As life expectancy continues to increase, it will be increasingly important that these potential prognoses be discussed well in advance of patients approaching their 75th birthdays.

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