Familial Longevity and Multi-Morbidities among the Elderly: A Study Using Multigenerational Pedigrees Linked to Medicare Diagnoses Files

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Abstract

Descendants from long-lived pedigrees have a significantly greater chance of living to advanced ages themselves. Examining the basis for this association is an active area of research. We address this issue by asking whether individuals from long-lived lineages are able to avoid one or two serious diseases associated with aging (notably heart disease and cancer, the most common lethal disease among the elderly) or whether these individuals benefit by having lower risks for a broad range of diseases. This latter prediction is consistent with the idea that persons with a strong family history of longevity are aging more slowly, a trait that reduces the risk of most age-related health conditions. These questions are examined based on a linked data set on nearly 120,000 persons age 65 and older; the data are derived by linking records from the Utah Population Database, Medicare (CMS) claims data from 1992-2002, and 2000 US Census information for Utah. We conclude that that a more favorable family history of longevity is protective against the risk of numerous major diseases. This result is also consistent with a previous analysis that found associations between increasing levels of familial longevity and lower risks for a large set of specific causes of death.

Introduction

There is a long history of research demonstrating strong familial aggregation in longevity (Finch & Tanzi, 1997; Graakjaer, Londono-Vallejo, Christensen, & Kolvraa, 2006; Herskind, McGue, Holm, Sorensen, Harvald, & Vaupel, 1996; Kerber, O'Brien, Smith, & Cawthon, 2001; Lunetta, D'Agostino, Karasik, Benjamin, Guo, Govindaraju et al., 2007; McGue, Vaupel, Holm, & Harvald, 1993; Mitchell, Hsueh, King, Pollin, Sorkin, Agarwala et al., 2001; Philippe, 1978). Individuals whose parents were longevous would themselves have a significantly greater chance of living to advanced ages. The mechanisms that form the basis for this association are not well understood. We begin to address this issue by considering a fundamental question: do individuals from long-lived lineages enjoy longer lives because they have a capacity to avoid one or two specific diseases associated with aging (notably heart disease and cancer, the most common lethal disease among the elderly) or do these individuals benefit by escaping a broad range of diseases? This question emphasizes the idea that familial resemblance in longevity may arise because of a general shared trait that both slows aging which in turn reduces the risk of many diseases.

The purpose of this study is to test the association between familial patterns of excess longevity and resistance to age-related chronic diseases among those over age 65. There are two competing hypotheses tested in this paper:

1) The Few: A family history of longevity reduces the risk of one or two major diseases suggesting that familial clustering of longevity is driven by some shared protective factor for selected major causes of death among the elderly.
2) The Many: A family history of longevity reduces the risk of a broad range of major diseases suggesting that familial clustering of longevity is based on a shared protective factor that slows rates of aging generally which in turn serves to reduce the risk of nearly all serious diseases experienced by elderly individuals.

These hypotheses will be tested using individual-level data on 118,825 elderly (65+) individuals identified from of a large population-based database. We examine whether a wide range of serious age-related medical conditions are less prevalent among members of long-lived families in relation to others in the population without a family history of exceptional longevity.

Data

The analyses are based on information obtained from the Utah Population Database (UPDB), one of the world's largest and most comprehensive computerized genealogically-based databases. In the 1970s, approximately 170,000 Utah nuclear families were identified on "Family Group Sheets" from the archives at the Utah Family History Library, each with at least one member having had a vital event (birth, marriage, death) on the Mormon Pioneer Trail or in Utah. These families have been linked across generations; in some instances, the genealogical records span seven generations (Bean,

Mineau, & Anderton, 1990; Mineau, Smith, & Bean, 2002; Smith, Mineau, & Bean, 2002). The UPDB records provide data on the original set of migrants to Utah and their Utah descendants (not only Mormons) that number more than 1.8 million individuals born from the early 1800s to the mid-1970's. The UPDB includes individuals who have lived in other states and countries and describes families with and without an affiliation to the Church of Jesus Christ of Latter-day Saints (LDS or Mormons).

The UPDB is actively creating family histories from newly linked records: new families and their members are continually being added as the UPDB is linked to other sources of data, including birth and death certificates. Additional information on these families comes from sources such as drivers' license records and the Utah Cancer Registry. Because these records include basic demographic information on parents and their children, fertility and mortality data are extensive with coverage up to 2006.

The UPDB has been linked in recent years to include information on morbidity events from population-based sources. Of central importance for this analysis is access to relatively complete medical records for the entire elderly population in Utah. To ascertain morbidity information on all covered elderly persons in Utah, we have used data from Medicare claims data. These data have been obtained from the Centers for Medicare and Medicaid Services (CMS) on Medicare-covered persons aged 65 or older and alive at any time between 1991 and 2002 in Utah.

Utahns represented in these data are those eligible for Medicare and age 65 or older. This covers individuals eligible for Social Security or Railroad Retirement benefits. Medicare has two key components, Medicare Part A and Part B. Part A is automatic and is fundamentally hospital insurance. Most people pay monthly for Part B which is optional and covers medical insurance. Part B helps to pay for doctors' services, outpatient hospital care, and some other medical services that Part A does not cover, such as the services of physical and occupational therapists, and some home health care. While Part B coverage is optional, 95 percent of those eligible choose to participate in Part B.

Key Variables

Familial Excess Longevity

We use a variable called Familial Excess Longevity (FEL) to measure of an individual's family history of longevity. FEL is an indicator, measured in years, of the average longevity of all blood kin of ego where these kin all lived to or past age 65. Constructing FEL for each kin requires two main steps. First, we measure individual-level excess longevity for all persons in UPDB who lived to age 65, defined as the difference between an individual's attained age and the age to which that individual was expected to live according to a model that incorporates basic predictors of gender and birth year. *Expected longevity* ($\hat{y}$) is estimated from an accelerated failure time (AFT) model and *excess longevity* (l) is $y - \hat{y}$, where y is the attained age in years (either at death or at the time last confirmed the relative was alive). Expected longevity ($\hat{y}$) is

based on the lognormal distribution and an AFT model was used because it provides a simple point estimate for duration and fit the obserevd data (Kerber et al., 2001). Excess longevity is then calculated for (typically hundreds of) blood relatives who reached the age of 65 for each ego. Averaging the excess longevities of all kin age 65 or older for each ego, with the appropriate weighting scheme, generates a point estimate of familial excess longevity. The kinship coefficient, the probability that an individual shares a particular allele with another individual, is used as a weight in calculating familial (Mendelian) excess longevity (FEL)(Kerber et al., 2001):

$$FEL_i = \frac{\sum_{k \in K} f(i,k) \cdot l_k}{\sum_{k} f(i,k)},$$

where FEL_i is the familial (Mendelian) excess longevity for subject *i, K* is the set of all blood relatives of subject *i* living to age 65, l_k is the excess longevity of the k^{th} member of K, and f(i,k) is the kinship coefficient. Quite simply, an individual with a higher value of FEL is someone whose blood relatives lived longer on average past age 65 and can be described as having a stronger family history of longevity.

Morbidity

A vast range of medical diagnoses are represented in Medicare claims data. In an effort to reduce this complexity we considered indexes that provide a workable and succinct list of key morbidity categories. We began by considering the Charlson comorbidity index which, in its original form, was created using clinical records (Charlson, Pompei, Ales, & MacKenzie, 1987). The index was based on the mortality of

604 patients from a New York hospital in 1984 after a one year follow-up. A weighted index was created that adjusted for the number and severity of numerous diseases was created. Nineteen diseases with a relative risk of 1.2 or higher were selected for the index. Relative risks were rounded to the nearest digit to create the weights.

The Charlson index was adapted for use with ICD-9 codes by Deyo et al (Deyo, Cherkin, & Ciol, 1992) and Romano et al (Romano, Roos, & Jollis, 1993). Deyo et al adapted the index for use with ICD-9 diagnosis and procedure codes. Romano et al included some diagnoses that were not in the original Charlson index. Both modifications were intended for use with the Medicare Part A records (Klabunde, Potosky, Legler, & Warren, 2000).

Klabunde et al (Klabunde, Warren, & Legler, 2002) created two indices, one for Medicare Part A records and one for Medicare Part B records. Introducing information from physician claims data significantly enhanced the index's predictive value for the risk of mortality. In the present study, we have adopted this variant of the Charlson comorbidity index based on the SEER-Medicare comorbidity SAS macros where all comorbid conditions are considered relative to a diagnosis of cancer. One of the two SEER-Medicare macros uses logic proposed by Klabunde and colleagues (Klabunde et al., 2000) where codes from clinical labs, diagnostic imaging, and medical equipment claims are excluded to maximize likelihood of the use of clinician-assigned codes. Codes are then examined at the patient-level and are excluded if a code appears only once in the year prior to the cancer diagnoses. Codes appearing multiple times in a 30 day time

frame, but never again are excluded. These exclusions help to provide some control for the differences in administrative reports and medical record.

A second SEER-Medicare macro calculates the comorbidity index with respect to cancer based on the Deyo adaptation of Charlson comorbidity index. Given that cancer is the index disease, it is not included as a comorbid condition in this SEER-Medicare program. The Deyo version of the Charlson index uses ICD-9-CM codes and two classifications not included in the Deyo version are cancer and metastatic carcinoma. They were not included because this macro is assuming that comorbidities are relative to cancer. Accordingly, we have added cancer and as a comorbid disease.

The many advantages of using CMS claims data for the assessment of co-morbidities are offset by some known limitations: left truncation of medical events, sensitivity of hospital claims data that vary by condition (Klabunde et al., 2002), and the limited number of diagnoses codes per claim which may lead to coding the most lucrative conditions (Klabunde et al., 2002). Also, co-morbidities *per se* may tend to be under-reported in administrative data (Quan, Parsons, & Ghali, 2002).

We have now linked 118,825 persons who appear in both the UPDB and the CMS records where are able to measure both FEL and comorbid conditions. We can identify specific episodes of the following 17 conditions occurring during the interval 1992-2002:

1. Myocardial Infarction
2. Congestive Heart Failure
3. Peripheral Vascular Disease

4. Cerebrovascular disease
5. Dementia
6. Chronic pulmonary disease
7. Rheumatologic disease
8. Peptic Ulcer Disease
9. Mild Liver Disease
10. Diabetes (mild to moderate)
11. Diabetes with chronic complications
12. Hemiplegia or paraplegia
13. Renal (kidney) disease
14. Any malignancy
15. Moderate or severe liver disease
16. Metastatic Solid Tumor
17. AIDS

We highlight the association between FEL and the risk of selected diseases in the tables. All of the diseases for which models were estimated appear in Appendix A. Note that for every condition considered, higher FEL was always protective. The counts for each condition are shown in Table 1.

Table 1 about here

Socioeconomic Status

The UPDB does not contain comprehensive information on indicators of socioeconomic status (SES) for all subjects. To measure SES, we linked CMS zip code data to 2000 US Census area SES measures. Persons in the CMS files have information on zip codes and these zip codes were linked to the 2000 US Census data at the zip code

level thereby providing key area-level SES measures for all zip-code-linked subjects: median family income and percent of families living below the poverty line. These SES measures may also be an indicator of access to health care where it is possible that lower SES neighborhoods have lower, not higher, risks of morbidity events because of less access to care and possibly under-diagnoses of serious conditions. When we restrict the sample to include persons with zip code data in the UPDB so that SES data can be added, we arrive at the final sample size of 118,825.

Table 2 shows descriptive statistics for all the covariates used in the analyses. Note that we divide the sample in this table into three general categories: those with both claims and at least one comorbid event, those with claims without any comorbid events, and those without any claims at all. The last group comprises the small percentage of persons who are explicitly identified as being enrolled in Medicare but have simply not made any claims for Medicare-covered services; these persons tend to be much younger (though still over age 65) and therefore enrolled in Medicare for fewer months.

Table 2 about here

Statistical Methods

For each morbidity category, a separate logistic regression was estimated where the dependent variable is whether the morbidity event occurred or did not occur during 1992-2002. The independent variables included FEL, gender, birth year, total number of months enrolled in Medicare Part A, total number of months enrolled in Medicare Part B, median family income, and percent of families living below the poverty line. The months-of-enrollment variables are included to control for the number of months of observation in the 1992-2002 interval. FEL was treated as a continuous variable in one set of models and as a categorical variable in another set. The categories comprise persons who are in the bottom 25%, middle 50%, and top 50% of the FEL distribution where the excluded category is the bottom 25%. The full details of all the models are shown in Appendix A.

OLS regressions are also estimated where the dependent variable is the number of morbid events. The range on this count variable is 0-13 with a mean of 1.53 conditions. The modal category is zero; these individuals included persons who had no Medicare claims or hade made claims but that did not include the 17 conditions considered here.

Results

Using logistic regressions that control for gender, areal socioeconomic status (median family income and percent of families in poverty in Census block group), birth

year, and years of observation, we estimated the odds ratios of being in the top 25% and middle 50% of the FEL distribution in relation to being the bottom 25%. We summarize the results in Table 3 and Figures 1 and 2. Given our very large sample size, p values are less informative since nearly all parameter estimates are significant (though if an association is insignificant, then we conclude that no association is present). We place more weight on effect sizes.

Table 3 and Figures 1 and 2 about here

We show that FEL is protective for nearly all major forms of morbidity, with the possible exception of cancer. This general pattern of protection for persons with greater FEL is consistent with the hypothesis that familial longevity is a general marker for slower aging where multiple health conditions happen less frequently or at a later age. Moreover, we observe a general dose-response relationship given that the protective effects of being in the top FEL quartile are larger than the protective influences of being in the middle 50% of the FEL distribution. We also show that persons in the highest quartile for FEL have a significantly lower risk of having any of the conditions considered here (i.e., dependent variable is "ever/never had any of the 17 conditions").

The fact that higher FEL levels, while still beneficial, have weaker protective effects for cancer risk is, in some respect, not an altogether surprising finding. Some have argued that the very mechanisms that slow aging may be the same as those that promote cancer (Bonafe, Barbi, Storci, Salvioli, Capri, Olivieri et al., 2002; O'Neill,

Nunez, & Melton, 2003; Serrano & Blasco, 2007). Specifically, the extraordinary ability for cells among some persons to survive and reproduce into very advanced ages is a basic mechanism that promotes a longer life but it is also similar to a mechanism (uncontrolled cell growth) that is the basis for cancer. Among the most prevalent site-specific cancers (breast, lung, colon, and prostate), FEL has a significant protective effect but only for lung cancer risk. At this point, it is unclear why this would be the case. We speculate that given our sample is from Utah, individuals with higher FEL may be active members of the Church of Jesus Christ of Latter-day Saints (LDS or Mormons) since it has been shown that Mormons have better adult survival probabilities (Mineau, Smith, & Bean, 2004). (The sample includes active, inactive and non-Mormons.) Accordingly, elevated FEL may be a proxy for being an LDS member and active members do not smoke tobacco, hence the lower lung cancer risk among those with high FEL. We do not observe any such protective large effects of FEL for the other major cancer sites -- lifestyle behaviors associated with the LDS church membership are less closely connected with the risks for these cancers (breast, prostate, and colon).

Table 4 shows the results of an OLS regression where the number of morbidity events is the dependent variable. The main result of this model is that persons in the highest quartile of FEL have, *ceterus paribus*, 0.4 fewer conditions than those in the lowest FEL quartile. This difference occurs on an average base of 1.53 morbid events, thus 0.4 fewer conditions represents a decline of nearly 25%.

Table 4 about here

From this model, and those using cause-specific logistic regressions, we find that individuals from census block groups with a higher percentage of families living in poverty have *lower* levels of morbidity. This association may reflect the fact that Medicare claims data provide information on both actual medical diagnoses but they also reflect access and use of health care. The positive association between neighborhood-level SES and risk of disease may therefore reflect lower access to medical care as well as quality of care for residents over age 65 living in poorer areas. Note that this association occurs whether we include in the models census block-group median family income (as shown) or not (not shown).

This linear regression includes as covariates the number of months enrolled in Medicare Part A and Part B to control for the effects of duration in the Medicare program. These two variables are found to have opposite effects: an increasing number of months in Part A reduces the number of conditions while an increasing number of months for Part B decreases it. This is a consequence of the collinearity between these two variables ($r = +0.90$). When only one but not the other enrollment-duration variable is included, we find that increasing duration increases the number of conditions. All variants of these models, where we include both duration variables or exclude one (logistic and OLS alike), do not alter the finding that higher FEL reduces the number of conditions.

Discussion

This analysis supports "The Many" hypothesis that a more favorable family history of longevity (higher levels of FEL) is protective against the risk of numerous major diseases. This is consistent with the idea that a positive family longevity history may slow the overall rate of aging since it reduces the risk of numerous diseases experienced by elderly individuals, not just the major causes of death, with a remarkable degree of consistency. This result is also consistent with a previous analysis examining the association between FEL and a large set of specific causes of death (O'Brien, Kerber, Smith, Mineau, Boucher, & Reed, 2007).

Medicare claims data represent an important opportunity for examining health events for entire populations over a relatively long period of time. Record linkage of these data to the UPDB provides a novel way to combine deep histories of one's lineage (e.g., longevity, fertility, causes of death) to contemporary medical events. The sheer coverage of individuals, family pedigrees, and medical records provides an excellent method for generating population-based estimates of the association between family health histories (including familial longevity) and the risk of adverse health conditions.

It is important to emphasize that for a minority, no apparent comorbid conditions were detected in the CMS records. While some conditions are possibly under-reported in these records, it raises the issue that some elderly are "escapees" in terms of avoiding a diagnosis of a serious adverse health event. These individuals may possess

characteristics, including some genetic variants, which allows them to reach age 65 and beyond with no major health conditions. Recruiting these individuals and appropriate controls would serve as an excellent basis for further investigations into mechanisms associated with exceptional survival and healthy aging.

Table 1. Counts of Morbidity Events Identified in CMS Data 1992-2002 based on an adaptation of the SEER-Medicare Version of the Charlson Co-morbidity Index		
Type of Morbidity	**N**	**Proportion (of 118,825)**
Ever Had a Comorbid Event	70953	0.597
Myocardial Infarction	7897	0.066
Old Myocardial Infarction	8165	0.069
Congestive Heart Failure	27934	0.235
Peripheral Vascular Disease	6216	0.052
Peripheral Vascular Disease With Surgery	1290	0.011
Cerebrovascular Disease	15895	0.134
Chronic Pulmonary Disease	19473	0.164
Dementia	6267	0.053
Hemiplegia or Paraplegia	3366	0.028
Diabetes (Mild to Moderate)	21933	0.185
Diabetes With Chronic Complications	7937	0.067
Chronic Renal Failure	3848	0.032
Mild Liver Disease	692	0.006
Moderate-Severe Liver Disease	410	0.003
Peptic Ucler Disease (Part1-Deyo Adaptation)	6624	0.056
Peptic Ucler Disease (Part2- Romano Adaptation)	2601	0.022
Rheumatologic Disease	5353	0.045
AIDS	10	0.000
Any Malignancy	18691	0.157
Metastatic Solid Tumor	4033	0.034
Breast Cancer	3319 (males and females)	0.028
Colon Cancer	1620	0.014
Lung Cancer	803	0.007
Prostate Cancer	7065 (of 54,332 males)	0.130

Table 2. 1992 - 2002 CMS Covariate Descriptive Statistics by Comorbid Subgroups (All Ages)

	At Least One Comorbid Event					One or More Medicare Claims but No Comorbid Event					No Medicare Claims				
Variable	**N**	**Mean**	**Std Dev**	**Min**	**Max**	**N**	**Mean**	**Std Dev**	**Min**	**Max**	**N**	**Mean**	**Std Dev**	**Min**	**Max**
Birth Year	70,953	1921.2	8.1	1892	1937	44,150	1927.2	7.7	1890	1937	3,797	1933.3	5.3	1893	1938
Male (=1)	70,953	0.464	0.499	0.000	1	44,150	0.431	0.495	0.000	1	3,797	0.633	0.482	0.000	1
FEL	70,953	2.105	2.169	-15.00	29.5	44,150	2.261	1.843	-14.90	22.9	3,797	2.189	1.799	-14.20	14
Median Family Income in Thousands	70,953	45650.5	10624.9	12639	87515	44,150	46771.2	11315.4	13750	87515	3,797	47938.7	12273.9	13750	87515
Total Number of Months Enrolled in Part A	70,953	106.9	31.3	0	132	44,150	87.0	43.9	0	132	3,797	37.4	38.5	0	132
Total Number of Months Enrolled in Part B	70,953	105.3	33.0	0	132	44,150	83.0	46.2	0	132	3,797	10.9	25.3	0	132
% of Families Living Below Poverty	70,953	0.095	0.061	0.000	0.621	44,150	0.091	0.063	0.000	0.621	3,797	0.088	0.063	0.000	0.424

Table 3. Odds Ratios for the Effects of FEL on Risk of Morbidity Events

	Middle 50% vs. FEL				Top 25% FEL			
	p	Odds Ratio	95% Wald Confidence Limits		p	Odds Ratio	95% Wald Confidence Limits	
Myocardial Infarction (MI)	0.00	0.81	0.77	0.86	0.00	0.68	0.64	0.73
Pre-Existing MI	0.00	0.77	0.73	0.81	0.00	0.61	0.58	0.65
Congestive Heart Failure	0.00	0.77	0.74	0.79	0.00	0.59	0.57	0.62
Peripheral Vascular Disease (PVD) (Atherosclerosis)	0.00	0.78	0.73	0.83	0.00	0.67	0.62	0.71
PVD with Surgery	0.00	0.80	0.71	0.91	0.00	0.62	0.53	0.73
Stroke	0.00	0.85	0.81	0.88	0.00	0.68	0.65	0.71
COPD (Chronic Obstructive Pulmonary Disease)	0.00	0.82	0.79	0.85	0.00	0.72	0.69	0.75
Dementia	0.00	0.84	0.78	0.89	0.00	0.68	0.64	0.74
Diabetes	0.00	0.79	0.76	0.81	0.00	0.64	0.61	0.67
Diabetes w/ Complications	0.00	0.75	0.71	0.79	0.00	0.62	0.58	0.66
Kidney Disease	0.00	0.82	0.76	0.88	0.00	0.69	0.63	0.75
Rheumatologic disease	0.00	0.90	0.85	0.97	0.00	0.82	0.76	0.89
All Cancers	0.00	0.93	0.89	0.97	0.24	0.97	0.93	1.02
Metastatic Cancer	0.00	0.86	0.80	0.93	0.25	0.95	0.87	1.04
Lung Cancer	0.00	0.62	0.52	0.73	0.00	0.72	0.60	0.86
Ever Having a Comorbid Event	0.00	0.76	0.74	0.79	0.00	0.62	0.60	0.65

Table 4. Regression Coefficients for the Effects of FEL on Number of Morbid Events				
Parameter Estimates				
Variable	**Parameter Estimate**	**Standard Error**	**t Value**	**p**
Intercept	127.86	1.42	89.90	<.0001
Male (=1)	0.34	0.01	35.63	<.0001
Median Family Income ($1,000)	-0.07	0.01	-11.64	<.0001
Birth Year	-0.07	0.00	-89.20	<.0001
Total Number Months Enrolled in Part A	-0.01	0.00	-18.30	<.0001
Total Number Months Enrolled in Part B	0.01	0.00	27.44	<.0001
% of Families Living Below Poverty	-0.92	0.11	-8.22	<.0001
Middle50% of FEL (=1)	-0.25	0.01	-20.44	<.0001
Top 25% of FEL (=1)	-0.41413	0.01343	-30.84	<.0001

Table 1- CMS 1992 - 2002: Relative Risk of Disease: Middle 50% of FEL vs. Bottom 25% of FEL (Controling for Gender, Age, Months in Cohort, and SES)

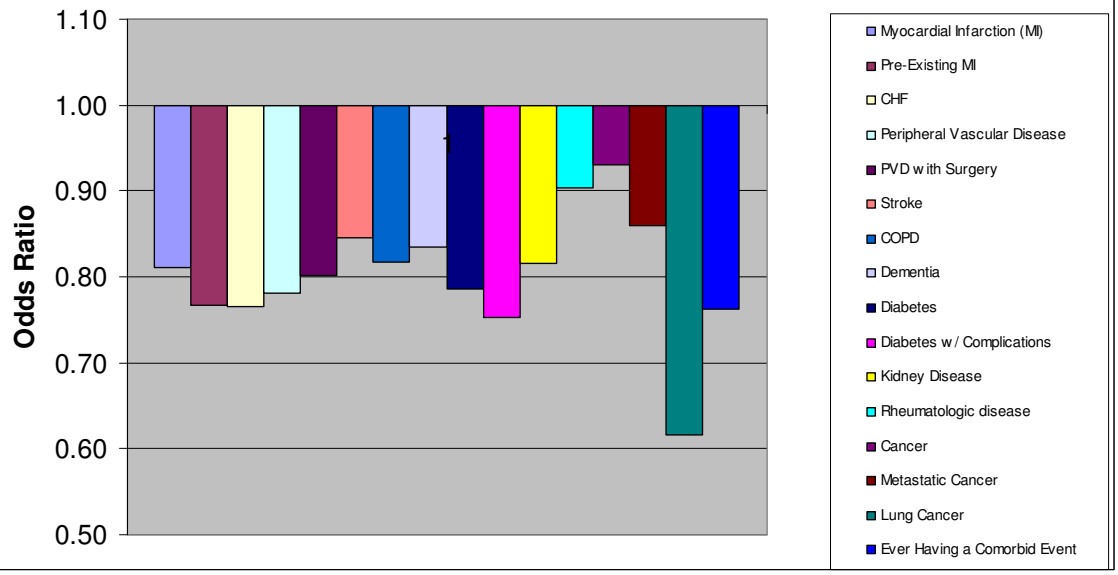
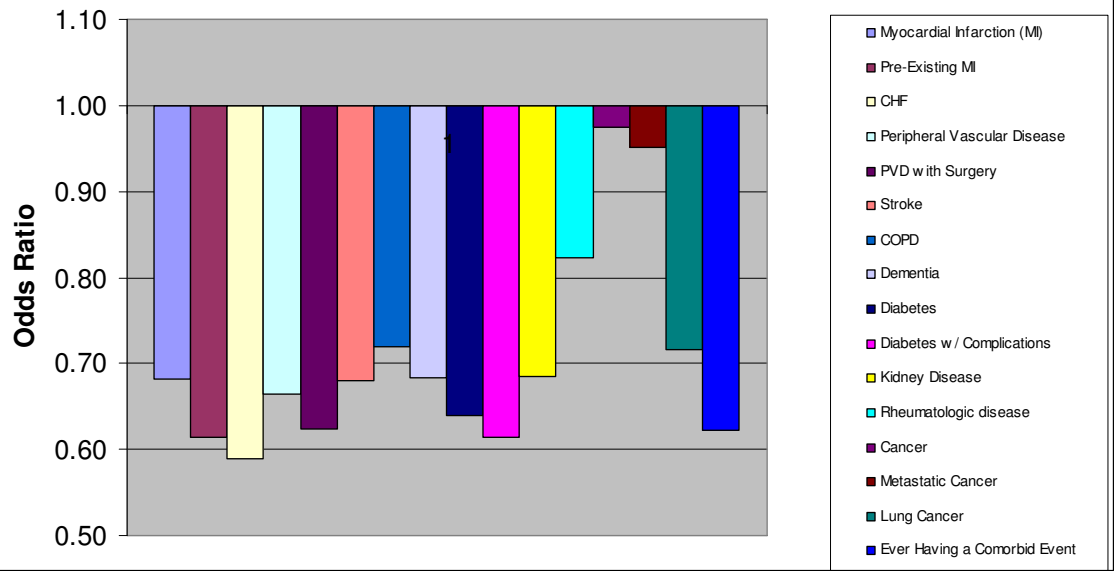


Table 2- CMS 1992 - 2002: Relative Risk of Disease: Top 25% of FEL vs. Bottom 25% of FEL (Controling for Gender, Age, Months in Cohort, and SES)



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APPENDIX A

Logistic Regressions for all Morbid Conditions
FEL is treated differently in 2 models – as a Categorical and as a Continuous Variable