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Dementia in Parkinson's Disease: Demographic Models and Estimates

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DEMENTIA IN PARKINSON'S DISEASE:

DEMOGRAPHIC MODELS AND ESTIMATES

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It is difficult to measure incidence and prevalence rates for rare conditions.[•] For very rare conditions, the sample size requirements begin to approach the total population size. However, there is a class of diseases for which it is possible, but very expensive, to conduct large population-based surveys. Some diseases in this category have been studied in only a few population-based studies. Often, even the largest studies produce estimates with very wide confidence intervals. In some cases we only have prevalence studies since they do not require longitudinal follow-up.

These studies typically produce estimates of single parameters related to the disease of interest (e.g., incidence, prevalence, or associated mortality). The prevalence of a disease in a population is the proportion of that population with the disease at a specific point in time. It is, by definition, a product of the incidence of the disease (the rate at which new cases arise) and the mean duration of disease, which is determined by rates of recovery and mortality. Many chronic diseases are believed to have recovery rates of zero; once affected by the disease, patients' symptoms and progression may be more or less well controlled, but they never return to a disease-free state. For these diseases, prevalence is determined exclusively by incidence of disease and the mortality associated with it.

Given the costs of estimating incidence and prevalence for many conditions, there are high returns to statistical analyses that improve our estimates of incidence and prevalence. In particular, we can learn a lot if we can combine data from incidence and prevalence studies. From individual studies of incidence, we can combine the prevalence rates from the baseline survey with the longitudinal incidence rates. Data from studies in different populations can be

[•] Incidence is the rate at which new cases appear in a population; prevalence is the proportion of the population affected by the disease at a specific time.

combined using meta-analysis techniques. However, data from different study designs that estimate different parameters cannot be combined with these methods. Demographic techniques, on the other hand, make it possible to combine data from heterogeneous study designs into a single model to refine the estimates derived from individual studies. In addition, we can address a broader range of demographic questions regarding the population impact of disease states.

Using a life table based method similar to that employed in Ewbank's study of Alzheimer's Disease as a cause of death in the United States (Ewbank, 1999), we integrated data from heterogenous studies to derive unified estimates of the effects of age, age at onset, and duration on the incidence and mortality associated with dementia among Parkinson's Disease (PD) patients. These estimates allow us to simulate the prevalence of dementia among PD patients by age, by duration, and by age at onset. We will present the methods as applied to the U.S. white female and male populations.

We will first outline the published research on the incidence, prevalence, and mortality of PD with dementia (PDD) in relation to age, age at onset of PD, and duration of disease. We will then describe the methods used to synthesize much of this data into a unified, demographic model. We will present the estimates for dementia incidence and mortality derived from that model and their implications for dementia prevalence by age, age at onset, and duration of PD. And finally, we will discuss the possible demographic and clinical implications of the results.

Background

PD and PDD fall into an intermediate category of diseases where it is possible, but difficult, to carry out incidence studies. PD is a neurological disorder associated with substantial and progressive movement disorders as well as some increased mortality. Although early students of the disease believed that it did not affect cognitive abilities, dementia has in recent decades been

recognized as one of the serious complications that frequently develops in the course of the disease. Because the disease affects less than one percent of the population, most research on PD has been clinic-based. However, there are well-known biases associated with the use of clinic-based samples in studying disease complications and progression. Cases that are referred to research-oriented clinical settings are often more severe and drawn unevenly across demographic groups. In addition, both PD and dementia may be undiagnosed in the population. The most unbiased estimates of PDD occurrence are therefore from studies that include appropriate examinations of population-based samples.

Such studies are difficult and expensive to conduct, and therefore relatively few and small. In addition, because PD incidence increases sharply with age, study results are very sensitive to the age distribution of the populations included. It is possible that apparent differences between populations or secular trends over time are simply reflections of differences in the age structure of populations. Prevalence studies, however, also offer potential insights into incidence and mortality rates. The prevalence of a disease state is a function of the rates of transitions into the state (incidence) and out of it (mortality).

We identified two population-based studies that estimated dementia incidence among PD patients (Rajput, et al., 1987; Marder, et al., 1995), two that estimated the excess mortality associated with dementia among PD patients (Ebmeier, et al., 1990; Louis, et al., 1997), and five that estimated dementia prevalence among PD patients (Aarsland, et al., 1996; Louis, et al., 1997; Marder, et al., 1995; Tison, et al., 1995; Wang, et al., 1996). These studies together included almost 1,300 PD patients. No single study included more than 323, and no one type of study included more than 604 patients.

These studies report disparate kinds of information, even within the categories of incidence, prevalence, and mortality studies. Some report age-specific data for 5- or 10-year age groups or other age groupings, some report only age-adjusted data. Some report on effects by age of onset of PD, or duration of PD, or both. In general, age at onset and duration were found either to be associated with higher dementia incidence or prevalence or to have no effect. Some studies report age effects only after adjusting for additional risk factors that may be age-associated. Prevalence of PDD among PD patients varies from 4.3% to 47% in different study populations.

Mathematically, age, duration, and age at onset effects cannot be estimated simultaneously, because the three variables are functions of each other (age at onset + duration = age). This "identifiability" problem has been discussed extensively in the epidemiologic literature in relation to the similarly inextricable trio of age, period, and cohort. Clinically, however, each variable has somewhat different implications. If duration of PD is positively associated with dementia incidence, dementia may best be viewed as one aspect of the natural progression of the disease. If age is most strongly associated with dementia, dementia within PD, like dementia in non-PD patients, may be related to other disease processes associated with aging. If dementia varies substantially with age of onset of the disease, that may suggest that PD with dementia is an etiologically-distinct variant of PD (Reid, et al., 1988).

We have modeled the data using age and duration of PD as variables, but our methods allow us to use age at onset data to fit the model, and to examine the results in relation to age at onset as well. Using life-table methods, we are able to examine the possibility that either or both of these variables affects the incidence of PDD, the relative risk of mortality associated with PD without dementia, and the relative risk of mortality associated with PDD.

Methods

We created a simulated multiple-decrement life table to examine the transitions from non-case to PD without dementia; from PD without dementia to PDD; and from each of the three states (no PD; PD without dementia; PDD) to death. We estimated a Weibull function for the age-specific incidence of PD (equation 1).

$$h(x) = ax^{b-1} \quad (1)$$

where h = probability of incident PD, x = age

Incidence of PDD was modeled as a linear function of age and duration of PD (equation 2).

$$D(x,d) = d + fx + gd \quad (2)$$

where D = probability of incident PDD given PD, d = duration We modeled the risk of mortality among non-demented PD patients (PDN) relative to non-PD patients as a linear function of age and duration of PD (equation 3).

$$R(x) = l + mx + Jd \quad (3)$$

where R = relative risk of dying, PDN vs. non-PD patients, m = probability of dying, non-PD patients.

The mortality risk among PDD patients relative to PDN patients was modeled as a linear function of age and duration (equation 4).

$$RD(x) = n + vx + qd \quad (4)$$

Using this model, we constructed simulated life tables for white females and white males age 40 to 100. We used the 1997 United States life tables estimates of the age-specific probabilities of dying (National Vital Statistics Report, 1999; Vol. 47, No. 28: Tables 5 and 6) as estimates of the age-specific probabilities of dying for white women and men free of PD. We estimated the eleven parameters described above (two age parameters for PD incidence and intercept, age, and duration parameters for PD mortality, dementia incidence, and dementia

mortality) simultaneously to maximize the joint likelihood of the observed data. The observations are those reported in 13 publications based on 11 different population-based studies of PD and/or PDD incidence, prevalence, and/or mortality (Table 1). For each published observation, the likelihood was calculated as follows:

$$L = C^n * (1 - C)^N \quad (5)$$

where L = likelihood, n = number of observed events, N = number of observed non-events, C = simulated proportion of events.

When the published results include mean age or mean age of onset of PD (with standard deviations) for cases and non-cases rather than age-specific counts of cases and non-cases, we calculated t statistics separately for cases and non-cases:

$$t = (\hat{m}_x - m_x) / s \quad (6)$$

where μ hat is the mean age of the study sample, μ is the simulated mean age from the life table model (or, in the case of data derived from a Norwegian sample, simulated mean age from the prevalences from the life table model applied to the age distribution of Norway from the 1991 Demographic Yearbook (United Nations, 1992), and s is the standard deviation of the study sample age.

The likelihood of the observations was then calculated as the p-value of each t-statistic.

All likelihoods were calculated separately for women and men, using data for women and men and the two separate life tables. The model was initially fitted with separate parameters for women and men. Likelihood ratio tests of each parameter were then conducted by setting the parameter to the null value to determine whether its inclusion significantly improved the fit of the model to the data. The model was re-estimated, and the likelihood ratio tests were repeated,

after the least-significant parameter was removed, until all remaining parameters were significant at the $\alpha = 0.05$ level.

The resulting age- and duration-specific estimates of PD and PD-dementia were then summed across durations to produce age-specific estimates of the incidence and prevalence of dementia among PD patients and across ages to produce duration-specific estimates of dementia incidence and prevalence within PD. We calculated age-at-onset (age minus duration) for each cell and summed across age and duration to estimate the incidence and prevalence of dementia by age at onset. We then calculated mean life expectancy and mean years of dementia-free life by age of onset of PD. Finally, we have applied the estimated prevalences of PD and PDD to the U.S. population to estimate the numbers of individuals with PD and PDD in the U.S. by age.

Results

The optimized parameters are shown in Table 2. Gender differences in the parameters examined were significant only for PD incidence: both the a and ß parameters for PD incidence were significantly lower for women than for men, implying a lower baseline incidence but a steeper increase with age.

Table 2

	Women	Men
PD incidence:		
alpha	0.0051	0.0037
beta	8	6
PDD incidence:		
baseline (age 70, duration 5)	0.1	0.1
age	0.0015	0.0015
duration	-0.001	-0.001
PD mortality (RR):		
baseline (age 70, duration 5)	1.2	1.2
age	-0.026	-0.026
duration	-0.008	-0.008
PDD mortality (RR):		
baseline (duration 5)	2.5	2.5
duration	-0.028	-0.028

These results confirm that, as anticipated, age was positively associated with the incidence of PDD among PD patients. Duration of PD, on the other hand, was negatively associated with PDD incidence. The excess mortality associated with PD without dementia, modeled as relative risk compared to the non-PD population, was modest (relative risk 1.2 at age 70, duration 5 years) and declined with both age and duration of PD. The relative mortality risk associated with PDD compared to the mortality of PD patients without dementia was substantially greater (relative risk 2.5). This risk declined with duration of PD, and was not significantly associated with age.

The simulated incidence of PD is higher among men at younger ages and higher among women age 84 and above (Figure 1), with mean age of onset 74 for women and 68 for men. Because of this pattern, the mean duration of PD among PD patients is greater for men than for women at the same age (the difference increases from 0.3 years at age 50 to 1.4 years at age 90). The mean age of women with PD is greater at any given duration of PD for the same reason. As as result even though the parameters for excess mortality and for dementia incidence do not vary by sex, the effects of the equations for PDD incidence and for excess mortality for PD with and without dementia (all of which incorporate duration of PD) are slightly different for women and men at the same age. We will therefore present all results separately by sex.

The simulated prevalence of PD by age (Figure 2) rises from less than 1 case per 1,000 before age 50 for men and before age 57 for women, to 10.0 cases per 1,000 men and 5.8 cases per 1,000 women age 70, to over 100 cases per 1,000 at age 98 for both sexes. Prevalence of PDD reaches 1 case per 1,000 men at age 58, and 1 case for 1,000 women at age 65. At age 70 the prevalence of PDD is 3.9 per 1,000 men and 2.0 per 1,000 women, rising to 20 per 1,000 at

age 92 for both sexes. Incidence of PDD among PD patients (Figure 3) rises less steeply, from about 7 cases per 100 at age 50 to 12 per 100 over age 95.

We can also look at PDD incidence and prevalence by duration of PD. PDD incidence per year (Figure 4) drops from 12 percent for women and 11 percent for men at duration 0 to 9 percent at durations over 40 years. In spite of decreasing incidence by duration of PD, prevalence of PDD rises steadily by duration, from 1 percent at 1 year duration to over 90 percent at 40 years duration (Figure 5). Both incidence and prevalence are slightly higher for women at each duration, because they are older than the men at the same duration of PD.

Because age of onset of PD is positively correlated with age and negatively correlated with duration of PD, incidence of PDD rises with age of onset of PD (Figure 6). This is more consistent with the theory that PDD represents a distinct disease process, present most often in late-onset PD, than with the view that dementia is part of the natural history of PD. Because of men's higher mortality rates, at each age of onset men have shorter mean duration of PD, and therefore their incidence of PDD is slightly higher than women's.

Prevalence of PDD drops steadily by age of onset of PD (Figure 7), because older patients have higher mortality and are more likely to die before developing PDD. Because women's mortality is lower, their prevalence of PDD is higher at each age of incidence, but the gap decreases at older ages of onset.

A noteworthy result of the simulation is the finding that mortality is increased very modestly by PD in the absence of dementia. Indeed, the simulation shows lower mortality for the non-demented PD patients 77 years old and above relative to the general population. Since a substantial proportion of the general population is affected by dementia, in that age group, this is not entirely implausible, although surprising. PDD, on the other hand, is associated with

substantial excess mortality. The patterns of age-specific mortality for PD and PDD patients are quite similar for women (Figure 8) and men (Figure 9) although the levels are higher for men, especially at the younger ages.

The Census Bureau estimates the total population of the U.S. ages 50 to 90 at 74,395,700. Based on the age-specific prevalences and associated mortality given by our simulation, we estimate that there are 6.9 cases of PD per 1,000 people in this age group, or 515,800 PD patients. Of these, 39% (198,900 people) have PDD. The simulation suggests that PD is responsible for 8,900 excess deaths per year among these patients, all due to excess mortality among PDD patients. The simulation's estimates that mortality rates among older PD patients without dementia are lower than among non-PD patients (some of whom have dementia) are responsible for this somewhat surprising result.

Finally, our simulation enables us to calculate life expectancies and expected years of dementia-free life for women and men based on age of onset of PD (Figure 10). The mean life expectancy for women with onset at age 50 is 26 years; women with onset age 70 have a life expectancy of 12 years. Men with onset at age 50 have a life expectancy of 21 years; those with onset at age 70, 9 years. However, because PDD incidence is high (between 6 and 15 percent per year), dementia-free life expectancy is substantially lower. This is particularly true for those with earlier ages of onset. Because their mortality is relatively low, but PDD incidence is high, these individuals are very likely to eventually suffer from dementia. Over 80% women and men with PD onset at age 50 will eventually progress to PDD, while fewer than half of those with onset at age 90 will do so (Figure 11). As a result, those with younger onset of PD have relatively little advantage in expected years of dementia-free life.

Table 3

	Mean dementia-free years	
Age of onset	Women	Men
40	12.9	12.3
50	10.3	9.7
60	8.2	7.5
70	6.5	5.8
80	4.9	4.4
90	3.4	3.2

Limitations

The limitations of the model must be remembered. We have used studies from nine countries on three continents, and assumed that, apart from differences in age and sex, there are no true population differences in any of the parameters we are studying. We have assumed, for the purposes of this model, that the prevalence of PD at age 40 is zero. PD before age 40 does occur, but it is extremely rare—none of the population-based studies we located identified any such cases. Age-specific data on the very old—especially those 90 and above—is sparse, and the estimates produced for those ages should be treated with caution.

As with conventional meta-analysis, we assume that the definitions and measurement of PD and PDD are comparable across the different studies. In this model, we have used data exclusively from population-based studies, but some defined PD and PDD based on medical record review rather than direct examinations, which allows for considerable variation in diagnostic practices and completeness.

Our model assumes that all incident PD cases are free of pre-existing dementia. Patients with pre-existing dementia who subsequently develop motor disorders will usually be diagnosed with conditions other than PD, distinguishing them from the PDD population. However, the one study we located that reported on dementia preceding PD diagnosis (Rajput, et al., 1987) reported that 5.9% of incident PD cases (and 3.0% of age-matched controls) were previously diagnosed with dementia. This study was based purely on review of medical records. It is possible that specialized examinations would not produce the same results.

Conclusion

By applying a life-table based simulation method to data from a wide variety of PD and PDD studies, we have been able to define a consistent set of parameters that define the age-related risks of PD, PDD, and PD-related mortality, and to describe the implications of these parameters for PD and PDD in the U.S. population. The results suggest that there are sex differences in the incidence of PD, with greater incidence among men at younger ages and women at older ages. In addition, our results show that excess mortality associated with PD without dementia is very slight, and primarily limited to younger PD patients, while there is substantial excess mortality associated with PDD.

We are also able to define life expectancies for women and men with PD, and to estimate the expected years of dementia-free life by age of onset of PD. We are not aware of any previous attempt to estimate life expectancies for PD patients. These estimates could not be derived without the application of a life-table based model.

These estimates are based on the limited population-based data available. One option to refine them is to include the results of clinic-based studies as well. Although these studies can introduce bias, the substantial quantity of additional data potentially available may outweigh that concern.

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Table 1

Outcome	Selected Results	Population	Authors and Year of Publication
PD incidence	Age 70-74: 67.0/100,000 PY (s.e. 14.6)	Japanese-American men, Honolulu	Morens, Davis, Grandinetti, et al., 1996
	Age-adjusted, white women: 11.8/100,000 (95% CI 5.9-17.8)	Northern Manhattan	Mayeux, Marder, Cote, et al., 1995
	Age-adjusted, white women: 17.5/100,000 (95% CI 14.3-20.7)	Rochester County, MN	Rajput, Offord, Beard, and Kurland, 1987
PD prevalence	Age 70-79, women: 12 / 722 (1.7%); men: 9 / 494 (1.8%)	Junin, Buenos Aires, Argentina	Melcon, Anderson, Vergara, and Rocca, 1997
	Age 70-79, women: 2 / 397 (0.50%); men: 2 / 311 (0.64%)	Kinmen, Taiwan	Wang, Fuh, Teng, et al., 1996
	Age 70-74, men: 32 / 5021 (6.4%)	Japanese-American men, Honolulu	Morens, Davis, Grandinetti, et al., 1996
	Age 70-74, women: 23 / 2231 (1.0%); men: 18 / 1925 (0.94%)	Rotterdam	de Rijk, Breteler, Graveland, et al., 1995
	Age 65-74, women: 32 / 7824 (0.41%); men: 31 / 4604 (0.67%)	Northern Manhattan	Mayeux, Marder, Cote, et al., 1995
	Age 65-74, women: 1 / 314 (0.32%); men: 1 / 228 (0.44%)	Starnberg, Germany	Trenkwalder, Schwarz, Gebhard, et al., 1995
PD mortality	Age 70-74, women: 198 (38 / 1000 PY); men: 300 (63 / 1000 PY)	Rome, Italy	Raschetti, Spila-Alegiani, Vanacore, et al., 1998
	Women: 112 / 127 cases, 170 / 250 controls	England & Wales	Ben-Shlomo and Marmot, 1995
PDD incidence	27 / 240 PY	Northern Manhattan	Marder, Tang, Cote, et al., 1995
PDD prevalence	134 / 288; PDD 47% women, PD no D 52% women	Northern Manhattan	Louis, Marder, Cote, et al., 1997
	67 / 242; mean age PDD: 78.7, mean age PD no D: 71.5	Rogaland County, Norway	Aarsland, Tandberg, Larsen, and Cummings, 1996
	Women: 1 / 10; men: 2 / 10	Kinmen, Taiwan	Wang, Fuh, Teng, et al., 1996
	Age 65-79: 1 / 22 (4.3%); age 80+: 15 / 22 (41%)	Gironde, France	Tison, Dartigues, Auriacombe, et al., 1995
PDD mortality	74 / 134 (55%) PDD; 24 / 154 (16%) PD no D	Northern Manhattan	Louis, Marder, Cote, et al., 1997

Figure 1

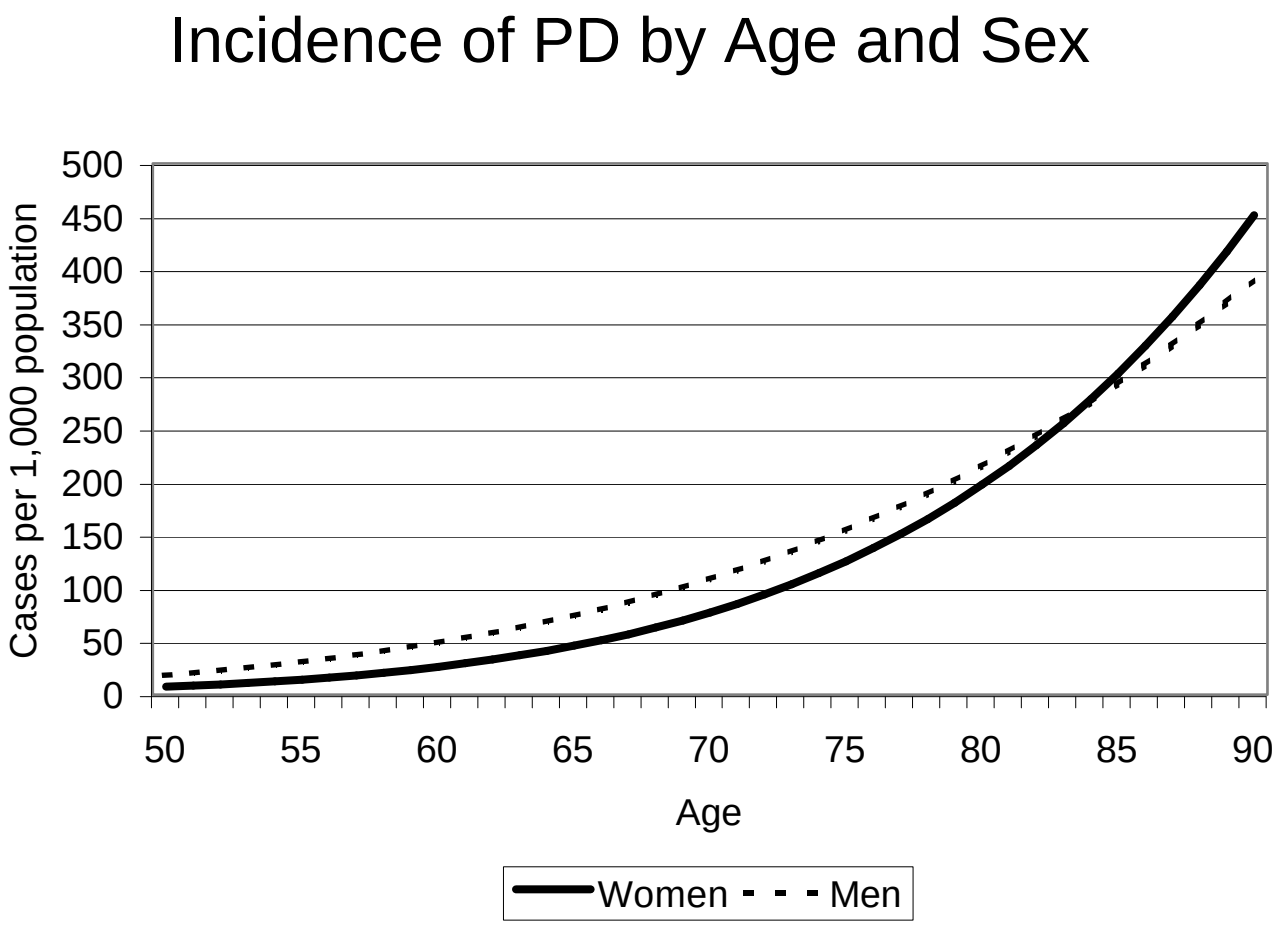

Incidence of PD by Age and Sex
Cases per 1,000 population
500
450
400
350
300
250
200
150
100
50
0
50
55
60
65
70
75
80
85
90
Age
Women
Men

Figure 2

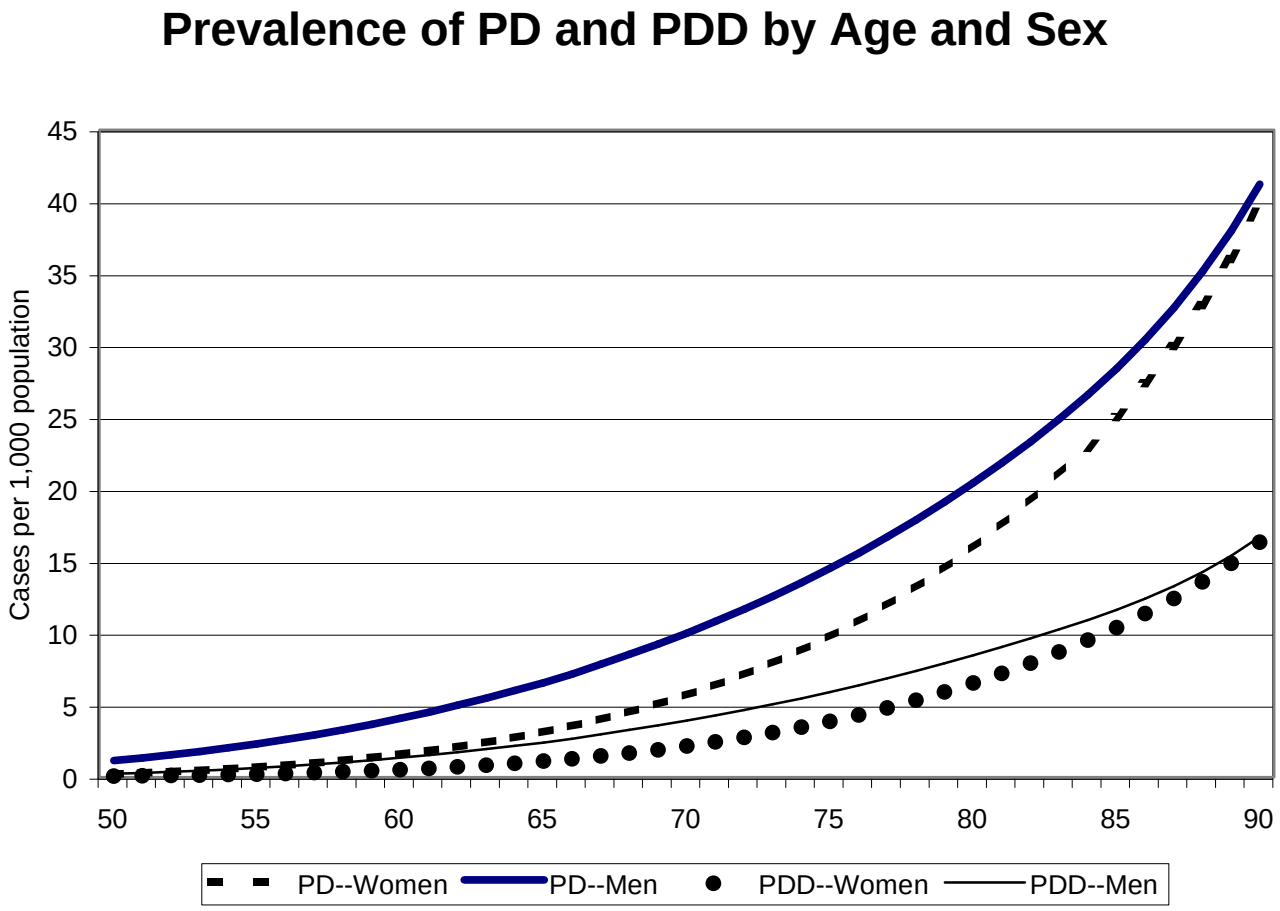

Prevalence of PD and PDD by Age and Sex
Cases per 1,000 population
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
PD--Women
PD--Men
PDD--Women
PDD--Men

Figure 3

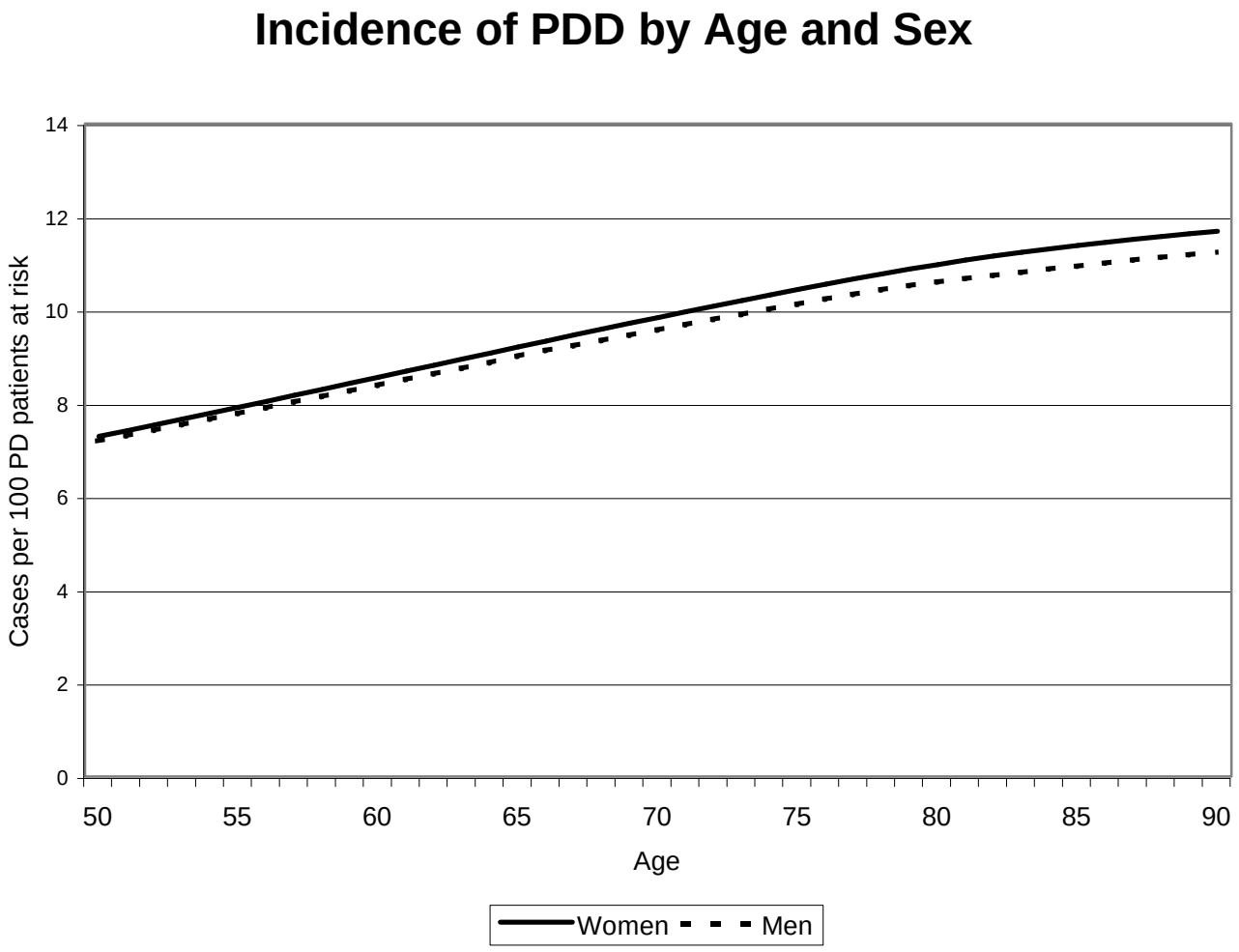

Incidence of PDD by Age and Sex
Cases per 100 PD patients at risk
0
2
4
6
8
10
12
14
50
55
60
65
70
75
80
85
90
Age
Women
Men

Figure 4

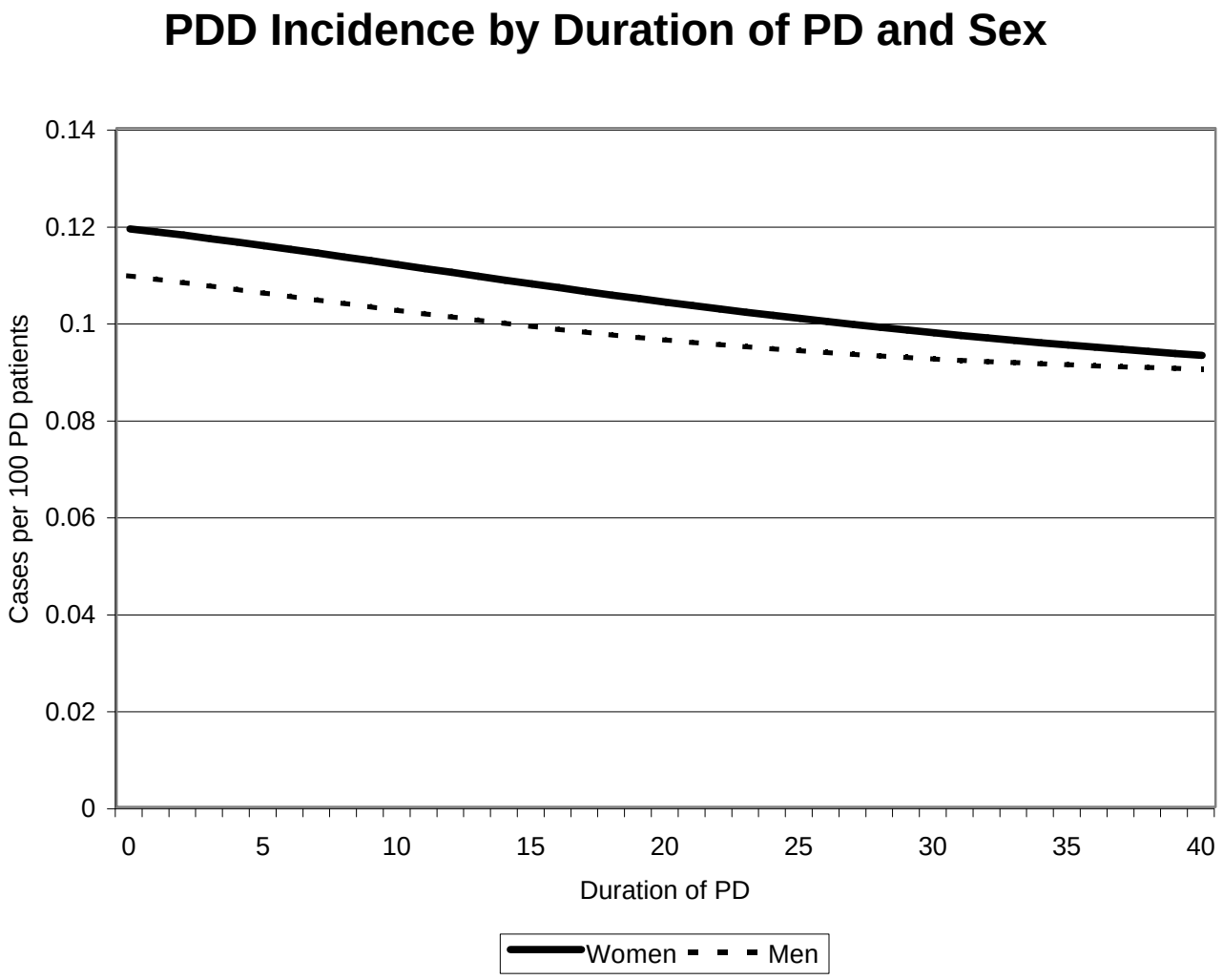

PDD Incidence by Duration of PD and Sex
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
Cases per 100 PD patients
0
5
10
15
20
25
30
35
40
Duration of PD
Women
Men

Figure 5

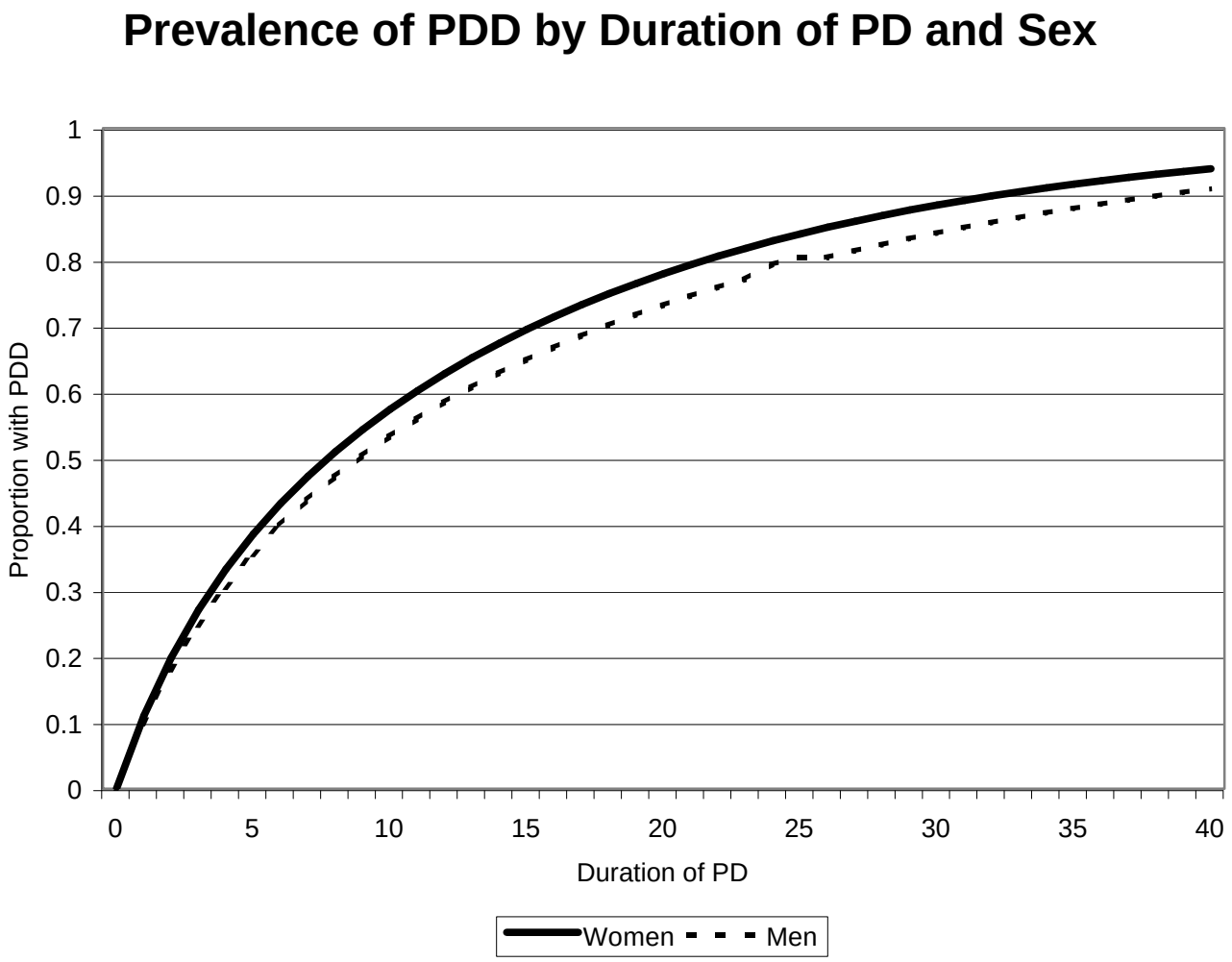

Prevalence of PDD by Duration of PD and Sex
Proportion with PDD
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
5
10
15
20
25
30
35
40
Duration of PD
Women
Men

Figure 6

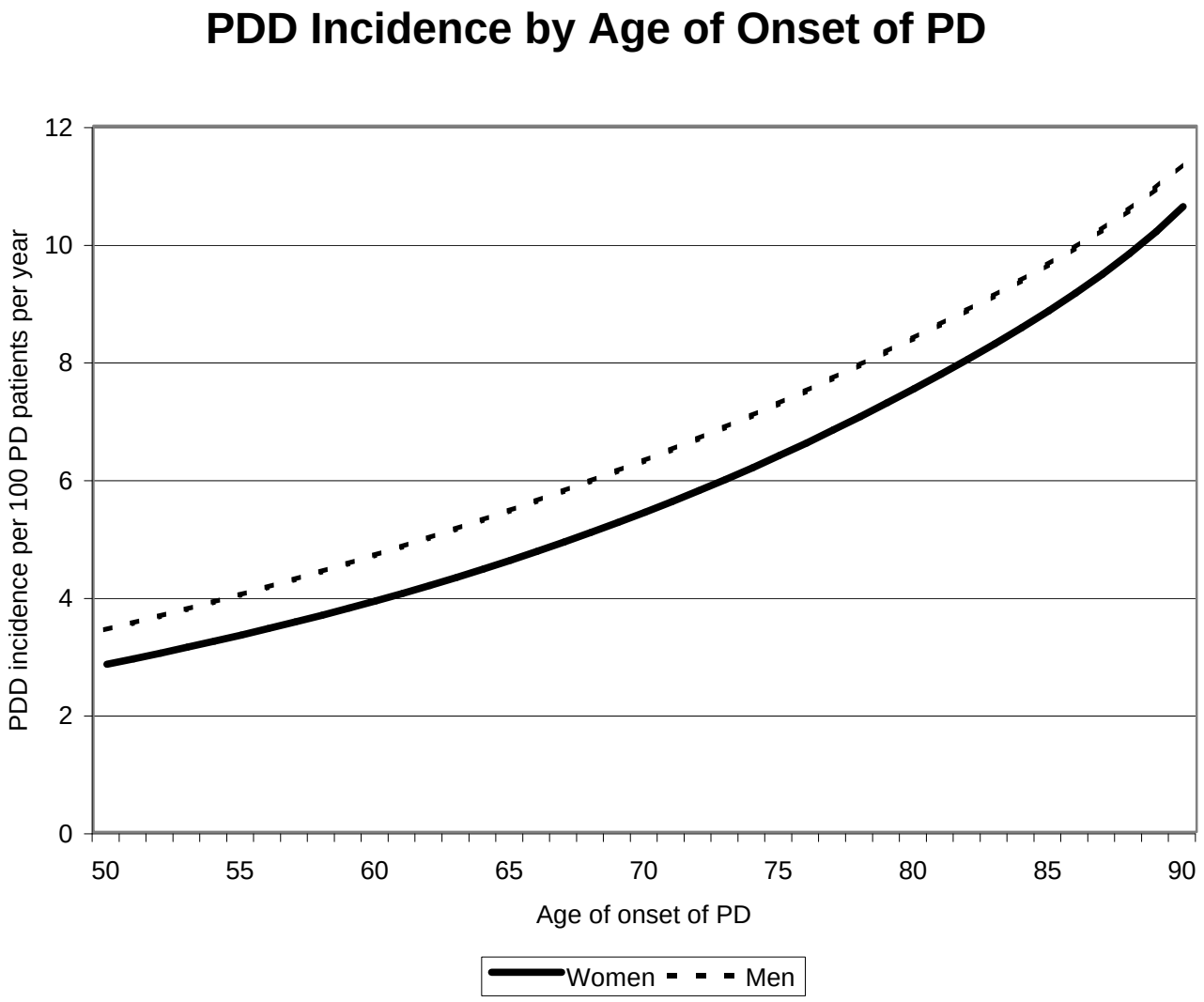

PDD Incidence by Age of Onset of PD
PDD incidence per 100 PD patients per year
0
2
4
6
8
10
12
50
55
60
65
70
75
80
85
90
Age of onset of PD
Women
Men

Figure 7

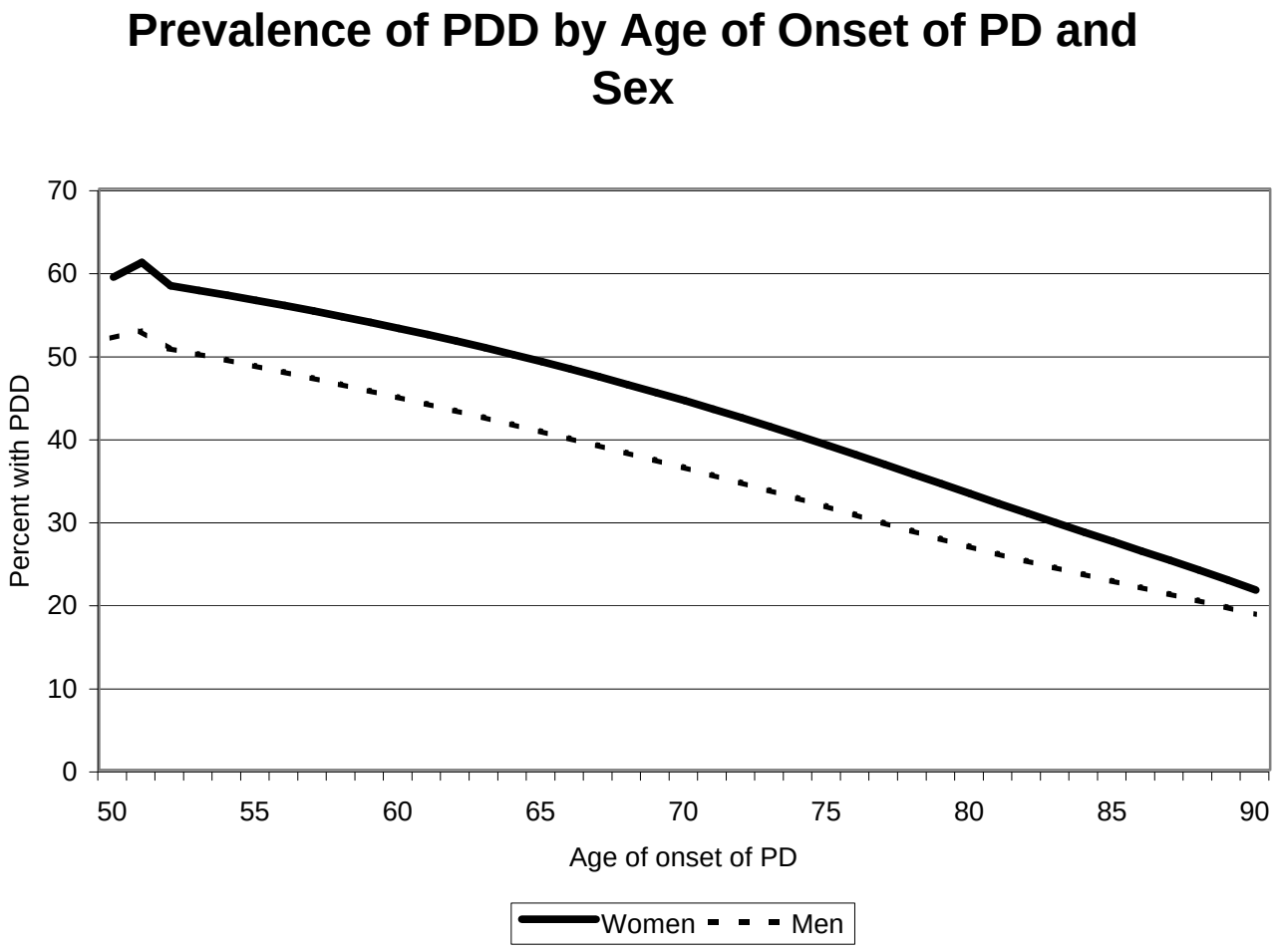

Prevalence of PDD by Age of Onset of PD and Sex
Percent with PDD
70
60
50
40
30
20
10
0
50
55
60
65
70
75
80
85
90
Age of onset of PD
Women
Men

Figure 8

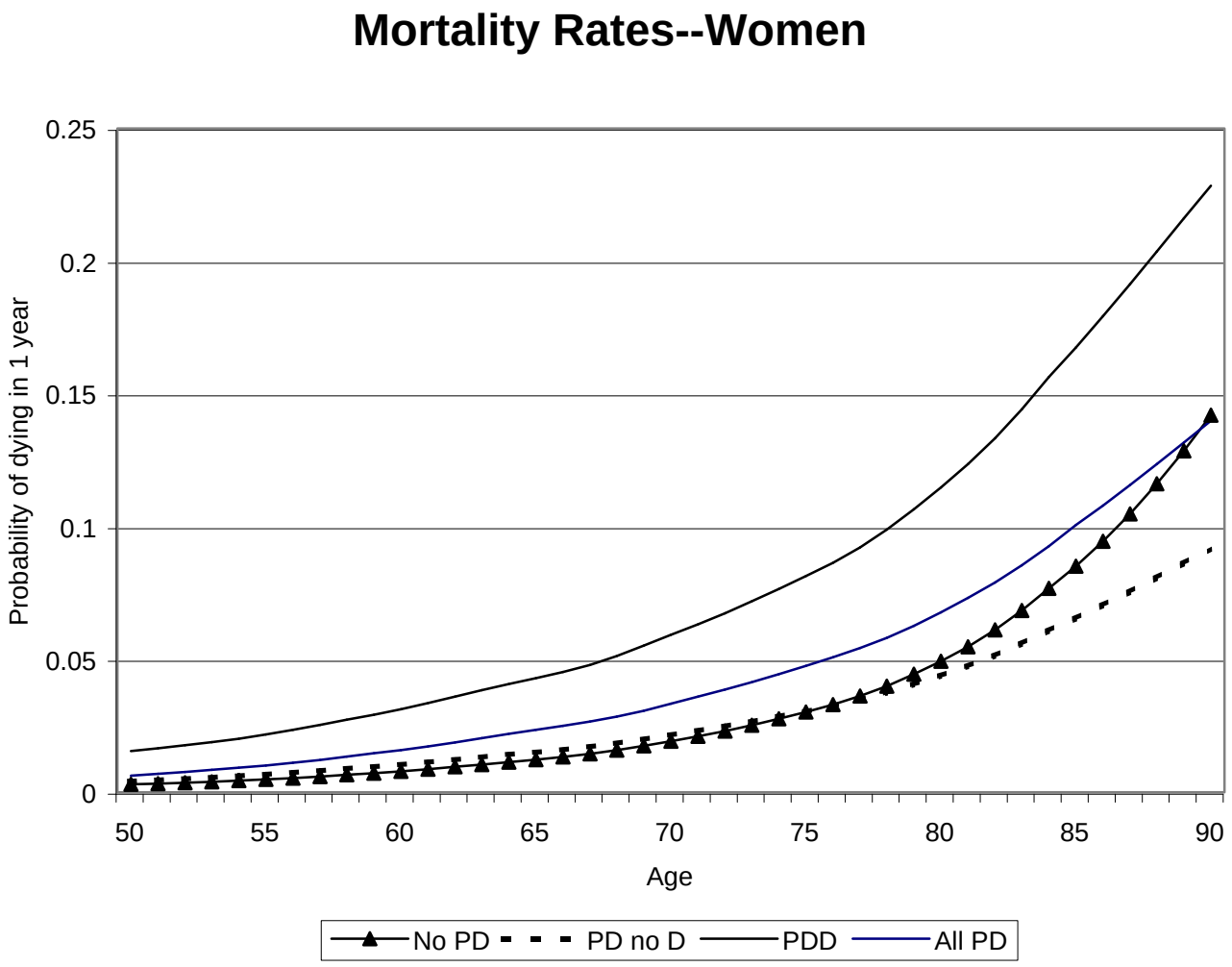

Mortality Rates--Women
Probability of dying in 1 year
0.25
0.2
0.15
0.1
0.05
0
50
55
60
65
70
75
80
85
90
Age
No PD
PD no D
PDD
All PD

Figure 9

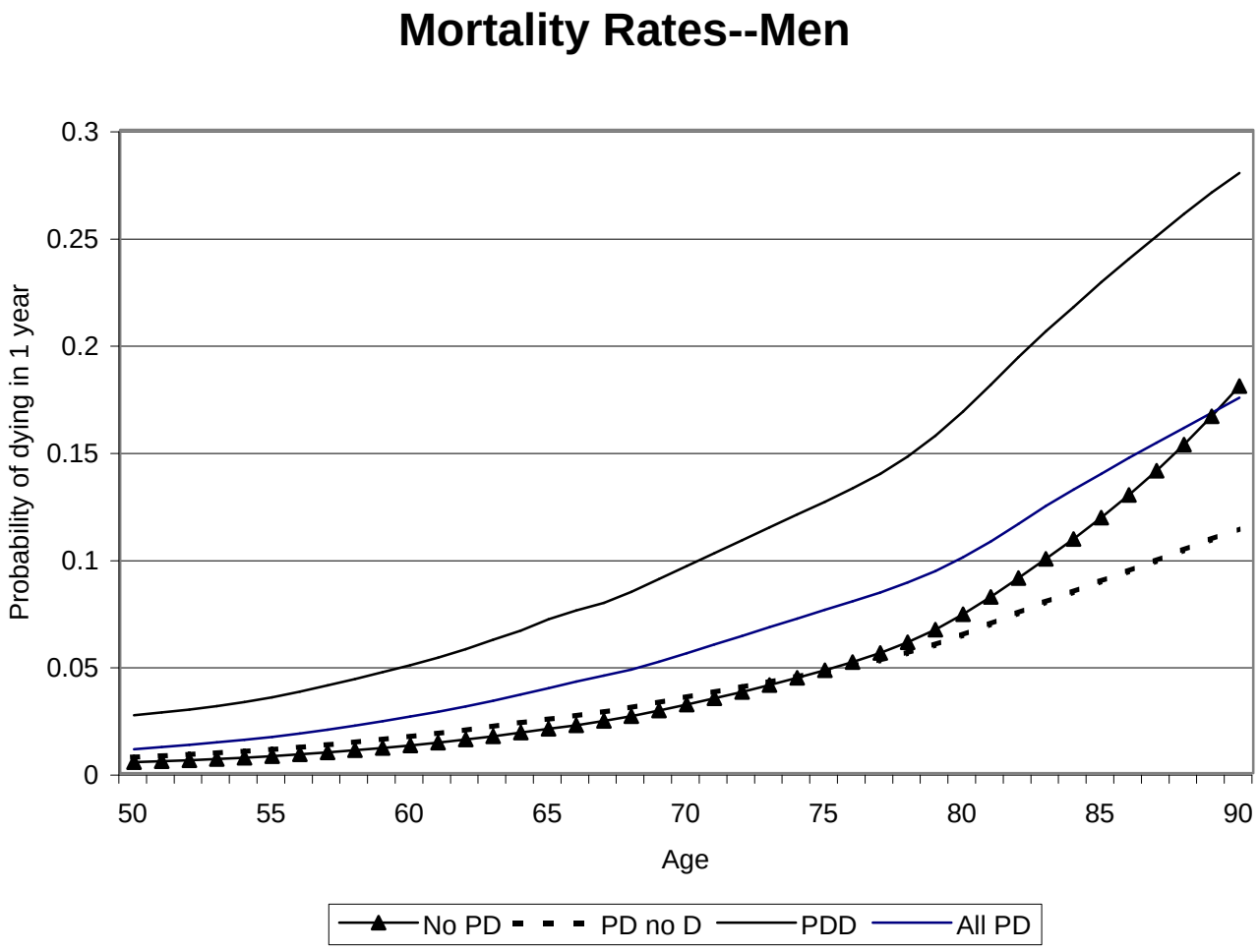
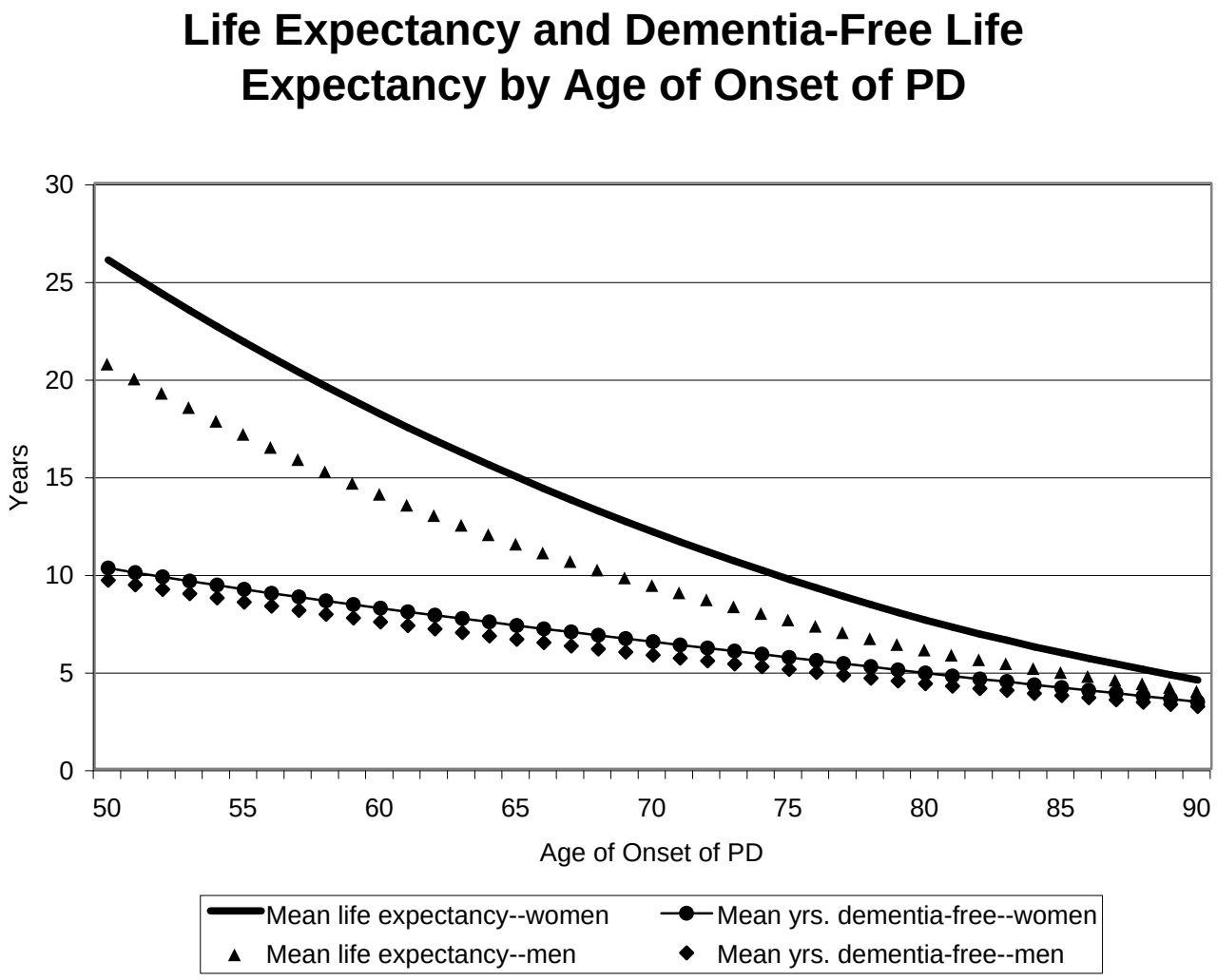

Mortality Rates--Men
Probability of dying in 1 year
0.3
0.25
0.2
0.15
0.1
0.05
0
50
55
60
65
70
75
80
85
90
Age
No PD
PD no D
PDD
All PD

Figure 10


Life Expectancy and Dementia-Free Life Expectancy by Age of Onset of PD
30
25
20
15
10
5
0
Years
50
55
60
65
70
75
80
85
90
Age of Onset of PD
Mean life expectancy--women
Mean yrs. dementia-free--women
Mean life expectancy--men
Mean yrs. dementia-free--men