Scientific Research

The Head Stands Accused by the Heart!

—Depression and Premature Death from Ischaemic Heart Disease

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Abstract

Background: The purpose of this study was to examine whether clinical depression was associated with higher risk of premature death from ischemic heart disease (IHD). Risk for IHD was examined separately by sex and sub-type of depression in a long-term follow-up study spanning 49 years. Method: Patients who were diagnosed with depression in the Chichester/Salisbury Catchment Area Study were followed for 49 years. Observed deaths from IHD prior to the age of 70 were compared with rates that were predicted from historical data on mortality rates from 1960 onwards. Results: Significantly higher rates of death from IHD before the age of 70 were found among males with endogenous depression. Conclusions: The results are discussed in terms of the broader literature on mortality from natural causes among patients with clinical depression. In terms of prevention, the results indicate that patients diagnosed with severe clinical depression particularly men at the very least warrant risk assessment with regard to IHD.

1. Introduction

Heart disease and depression are both very significant contributors to the global burden of mortality and morbidity. WHO currently estimates that 7.3 million deaths are due to heart disease annually and that depression affects 350 million people globally in any one year. Mounting evidence from clinic-based and community samples suggest that individuals suffering from severe depression are at increased risk for death from natural causes. Higher rates of mortality from natural causes in depressed individuals have been found in large-scale community-based investigations conducted in rural Canada (Murphy, Monson, Oliver, & Leighton, 1987), the United

States (Bruce, Leaf, Rozal Florio, & Hoff, 1994; Kouzis, Eaton, & Leaf, 1995; Zheng, Macera, Croft, Giles, Davis, & Scott, 1997), Norway (Mykletun, Bjerkeset, Øverland, Prince, Dewey, & Stewart, 2009), and the United Kingdom (Surtees, Wainwright, Luben, Wareham, Bingham, & Khaw, 2008; Thomson, 1996; Thomson. 2011). In order to more fully understand the processes linking clinical depression with mortality, investigators have examined the association of depression with specific diseases. Particular attention has been given to the relationship of depression with death from cardiovascular illness. Systematic reviews and meta-analyses of research suggest that depression substantially increases the risk of death from cardiovascular disease among individuals who initially do not show overt symptoms of cardiovascular impairment (Nicholson, Kuper, & Hemingway, 2006; Rugulies, 2002; Wulsin, Evans, Ramachandran, Murabito, Kelly-Hayes, & Benjamin, 2005; Wulsin, Valliant, & Wells, 1999), even when the effects of smoking, obesity, and other risk factors are controlled (Surtees, Wainwright, Luben, Wareham, Bingham, & Khaw, 2008; Aromaa, Raitasalo, Reunanen, Impivaara, Heiovaara, Knect, Lehtinen, Joukamaa, & Naatreka, 1994; Pratt, Ford, Crum, Armenian, Gallo, & Eaton, 1996; Wulsin, & Singal, 2003). The present study will seek to increase our understanding of the association between clinical depression and premature death from IHD by considering the degree to which the strength of this relationship may differ by sex and depressive subtype, and by utilizing a long-term follow-up period spanning 49 years.

The present study examines potential differences in the strength of the association between clinical depression and IHD death by sex. While studies of depression as a risk factor for IHD often control sex differences in depression and IHD, they rarely examine the possibility that the association between depression and IHD may be stronger for men or for women. The preponderance of available evidence suggests that the effects of depression and anxiety disorders on IHD mortality may be stronger for men than that for women (Murphy, Monson, Oliver & Leighton, 1987; Aromaa, Raitasalo, Reunanen, Impivaara, Heiovaara, Knect, Lehtinen, Joukamaa, & Naatreka, 1994; Coryell, Noyes, & Clancy, 1982; Haugland, Craig, Goodman, & Siegel, 1983; Hoyer, Mortensen, & Olesen, 2000; Lawrence, Holman, Jablensky, & Hobbs 2003; Rorsman, 2007; Week & Vaeth, 1986), although this finding has not been replicated in all studies (Angst, Stassen, Clayton, & Angst, 2002; Osby, Brandt, Correia, Ekborn, & Sparen, 2011; Tsuang, Woolson, & Fleming, 1980).

The present study will also examine the possibility that certain types of depression are more closely associated with increased risk for premature death. In the broader literature on depression and premature death, higher rates of death from natural causes have been found among patients with endogenous depression (Thomson, 1996), but not those with reactive depression. By contrast, in the literature on IHD mortality, potential differences in mortality between patients with reactive and endogenous forms of depression have not received attention. Rather, in IHD research, consideration of the heterogeneity of depression has focused on differences between unipolar and bipolar patients (Angst, Stassen, Clayton, & Angst, 2002), or differences in mortality associated with the duration or severity of depressive symptoms (Wulsin, Valliant, & Wells, 1999; Coryell, Noyes, & Clancy, 1982).

The present study will focus on premature death from IHD mortality across an extended follow-up period. In the context of trends in life expectancy and IHD mortality in the past 50 years, death from IHD before the age of 70 years merits attention. Between the 1970's and 2000, mortality rates from IHD for individuals under the age of 70 declined (Allender, Scarborough, O'Flaherty, & Capewell, 2008). To the extent that depression is associated with increased risk of premature death from IHD, we would expect to find that rates of IHD death among depressed individuals are higher than the rate predicted by declining trends. To more adequately assess the incidence of premature IHD death, and its association with depression, the present study will utilize an extended follow-up period. Characteristically, investigations of IHD mortality have followed subjects for fewer than ten years. However, initial investigations that have employed a longer follow-up period (Murphy, Monson, Oliver, & Leighton, 1987; Angst, Stassen, Clayton, & Angst, 2002) suggest that the association between clinical depression and IHD mortality may span multiple decades. The present investigation will follow IHD deaths up to 49 years after the initial diagnosis of depression. Such an extended time frame enables the investigator to detect such phenomena as premature IHD death in middle age among patients who have been diagnosed with depression in young adulthood. The focal hypotheses to be tested in the present investigation posit the following:

Hypothesis 1: Men with endogenous depression will be at higher risk of premature IHD death than men of comparable age in the general population.

Hypothesis 2: The association between depression and premature IHD death will be stronger among patients who have been diagnosed with endogenous than reactive depression.

2. Methods

2.1. Participants and Procedures

The sample for the present study is a longitudinal extension of the one that was utilized in the Thomson (Thomson, 1996) 24-year follow-up study of depression and premature mortality. In the present work, the timeframe for the investigation was extended from 24 to 49 years. Permission was granted to use the data collected by Sainsbury and colleagues (Sainsbury, Walk, & Grad, 1966) to evaluate community care in two distinct health authorities in England. The present study utilizes data from subjects who have been formally diagnosed with depression by psychiatrists: clinical severity, rather than being categorized as depressed based on self-report survey screening measures, thereby implying severity. The total population of patients referred to the two catchment areas was 1413, of whom 685 were diagnosed as depressed (480 were diagnosed as having endogenous depression, and 205 were diagnosed as having neurotic reactive depression). The mean age of patients with reactive depression was 44 compared with 58 years for the patients with endogenous depression. Males formed 33.3% of the total cohort, with a mean age at referral of 58.1 years. Females formed 67.7% of the total population, with a mean age at referral of 51.2 years. The theory that depression was either endogenous or reactive in origin was still prevalent in 1960 when the original data was collected, this theory has since lost support. It is now commonly believed that both environmental and genetic history play a part. Because the present study utilized actuarial information about age adjusted death rates, cases were included only if the date of birth and death could be ascertained. In addition, cases younger than 16.5 years of age at the start of the study were not included. Of the 685 cases that formed the original cohort, 566 were utilized for the present study based on the availability of birth and death dates, as well as meeting the age criterion for inclusion.

2.2. Measures and Procedures

Four research psychiatrists made diagnoses of reactive and endogenous depression. A consultant to the research unit then made an independent diagnosis of each case on a separate visit. The resulting diagnoses have been found to be reliable and to possess high levels of diagnostic convergence (Kreitman, Sainsbury, Morriset, Towers, & Scrivener, 1961). Further information concerning the diagnostic procedures has been reported earlier (Sainsbury, Walk, & Grad, 1966). The Chichester and Salisbury samples focused on patients with a primary diagnosis of depression, not depression secondary to physical illnesses such as IHD.

2.3. Endpoint

Information regarding the date and cause of death was collected through the National Health Service Register (NHSCR). A protocol was submitted to the NHSCR to obtain permission to use these data in the study. Once the protocol was accepted, information from each patient was put on two cards. One card was sent to the NHSCR the other was retained. Records of each patient were returned, with the data and cause of death together with the International Classification of Disease code. Cases were coded as IHD deaths using the same ICD codes as those published by Allender and colleagues (Allender, Scarborough, O'Flaherty, & Capewell, 2008). Individuals whose cause of death included IHD or IHD and another cause of death were counted as IHD Deaths.

2.4. Analysis

The present study compared observed IHD death rates in this cohort of patients with normative data from the entire population of England and Wales that was collected by the Office of Populations and Surveys (OPCS) and subsequently analyzed in a study of trends in IHD deaths in the past fifty years (Allender, Scarborough, O'Flaherty, & Capewell, 2008). These tables provided information on the national rate of IHD death by age and sex for each year of the study. Particular attention was given to death rates for individuals under the age of seventy. For each year of the study, the expected number of deaths was computed based upon the distribution of cases by age and sex.

3. Results

Analyses were conducted in two stages. Exploratory analyses examined the age of death from IHD and other natural causes among men and women with reactive and endogenous depression, as well as the relative fre-

quency of death from IHD and other natural causes among individuals under the age of seventy. These exploratory analyses suggest that premature IHD death may be more common among men with endogenous depression. The main analyses of the present study examined the frequency of premature IHD death by sex and type of depression in relation to expected levels of IHD death in the general population. Predicted and observed rates of IHD death were compiled for each year of the study by sex for patients who were initially diagnosed as having reactive or endogenous depression. Because almost all of the patients diagnosed with endogenous depression had died or reached the age of seventy by the fortieth year of the study, a relatively small sample was available between 2000 and 2009. Hence, the analyses focused on data from 1960 through 1999.

3.1. Exploratory Analyses

Exploratory analyses examined the timing of IHD death, and the relative incidence of IHD death, by sex and type of depression. **Table 1** shows the number of deaths from IHD and all other causes for men and women with reactive and endogenous depression over the course of the forty-year follow-up. While deaths from IHD occur frequently across all groups, the age of death from IHD is lower among men with endogenous depression (M = 69.5) than the age of death from other natural causes. **Table 2** shows the number of deaths before the age of 70 from IHD and all other natural causes for men and women with reactive and endogenous depressives. IHD is the leading cause of IHD death among men with endogenous depression: half of deaths arise from IHD. By contrast, IHD accounted for only 18.7% of the premature deaths among women with endogenous depression, and 19% of the premature deaths among men with reactive depression. While these findings are consistent with the view that risk for premature death is higher among men with endogenous depression, more rigorous analysis is needed to determine whether premature IHD death rates are higher in this group than in the general population. This question will be addressed in the following section.

3.2. Main Analyses: Observed and Expected IHD Mortality Rates

The main analyses of the present study computed predicted IHD death rates before the age of 70 for this sample. As described above, predicted death rates were computed based upon a published analysis of mortality data (Allender, Scarborough, O'Flaherty, & Capewell, 2008). **Table 3** shows the number of predicted and observed deaths for reactive and endogenous depressives between 1960 and 1999. To determine whether the observed frequency of deaths is significantly higher than the predicted frequency, the Poisson test (Rosner, 2005) was employed. The null hypothesis stated that the observed frequency of deaths over this forty year period was the same as a proportion of cases that would die in the general population based on the sex and age distribution of the sample in each year of the study.

Consistent with Hypothesis 1, the association between depression and premature IHD death was stronger for men than for women. The Standardized Mortality Ratio (SMR) for men was 1.97, while the SMR for women was 1.15. Hypothesis 2 was partially supported. The incidence of IHD death was significantly higher than for males with endogenous depression than it was for men of the same age. However, the incidence of IHD death was not significantly higher for women with endogenous depression, or for patients with reactive depression.

4. Discussion

The results of the present study support the hypothesis that endogenous depression is associated with higher risk for IHD among men. Men in this group have almost twice as much risk of dying from IHD before the age of seventy than their counterparts in the general population. These findings further suggest that the pathways linking depression and IHD mortality may vary depending upon sex and the type of depression: men with endogenous depression were particularly prone to premature death from IHD. The finding of elevated levels of premature IHD mortality among men with endogenous depression is consistent with earlier findings of elevated IHD mortality among men who have suffered from clinical depression (Murphy, Monson, Oliver, & Leighton, 1987; Aromaa, Raitasalo, Reunanen, Impivaara, Heiovaara, Knect, Lehtinen, Joukamaa, & Naatreka, 1994; Coryell, Noyes, & Clancy, 1982; Haugland, Craig, Goodman, & Siegel, 1983; Hoyer, Mortensen, & Olesen, 2000; Lawrence, Holman, Jablensky, & Hobbs, 2003; Rorsman, 2007; Week & Vaeth, 1986), although it also raises the question of whether failures to replicate this finding (Angst, Stassen, Clayton, & Angst, 2002; Osby, Brandt, Correia, Ekborn, & Sparen, 2011; Tsuang, Woolson, & Fleming, 1980) might be explained in part by differ-

Table 1. Lifespan by sub-type of depression, sex, and cause of death (excluding suicides).

Type of Depression	Sex	Cause of Death	Lifespan (Years)		
			M	SD	n
Reactive	Male	IHD	71.9	10.91	7
		Other	69.6	8.95	20
	Female	IHD	76.9	8.44	14
		Other	74.7	10.47	34
Endogenous	Male	IHD	69.5	10.59	34
		Other	75.1	10.12	83
	Female	IHD	77.5	9.57	35
		Other	76.8	11.10	172

Table 2. Frequency of death before age of 70 from IHD and other natural causes by sub-type of depression and sex.

Type of Depression	Sex	Cause of Death			
		IHD		Other Natural Causes	
		n	%	n	%
Reactive	Male	2	19.2%	9	81.8%
	Female	3	25.0%	9	75.0%
Endogenous	Male	18	50.0%	18	50.0%
	Female	6	18.7%	26	81.3%

Table 3. Observed and expected IHD deaths before age of 70 by type of depression and sex (40-year follow-up).

Type of Depression	Sex	Observed	Expected	p	SMR
Reactive	Male	2	2.49	0.710	0.80
	Female	3	2.00	0.323	1.50
Endogenous	Male	18	9.12	0.006	1.97
	Female	6	5.23	0.424	1.15

ences in the sub-types of depression that are included in the study. The results of the present study suggest that sex differences are not as evident among patients who would be characterized as having reactive depression. The finding of elevated mortality among men with endogenous depression is also of interest given the findings of research on death from natural causes in this cohort (Thomson, 2011). This broader study found that clinical depression was associated with higher rates of premature mortality from natural causes for men and women, but that this association was stronger for women than for men (Thomson, 2011). This pattern of findings suggests that the linkage between depression, sex, and premature mortality from natural causes may differ depending upon the specific cause of death that is under consideration. Premature death from IHD may be a greater concern for depressed men, while levels of premature death from other natural causes may be more prevalent among depressed women.

The results of the present study illustrate the value of using long-term follow-up periods to investigate the association between depression and mortality from specific causes. The potential benefit to using a thirty or forty-year follow-up period is the opportunity to record the causes of mortality for almost all of the members of a cohort, thereby gaining more data on the health consequences of depression (Murphy, Monson, Oliver, & Leighton, 1987; Angst, Stassen, Clayton, & Angst, 2002). Research conducted with briefer follow-up periods may underestimate the effects that chronic depression has on health problems that emerge decades after the initial diagnosis of depression is made.

The results of the present investigation suggest further directions for future research. A logical next step in accounting for the connection between endogenous depression and premature IHD death among men would in-

volve examining the incidence of IHD risk factors in this patient population. To the extent that men with endogenous depression are more likely to engage in unhealthy behavior (excess eating, drinking, smoking; overeating and obesity; poor compliance prescribed medications or other treatments to address cholesterol levels), the link between endogenous and depression and premature IHD death may be explained, and addressed by these behavioral factors. While increased levels of these risk factors have been found among depressed individuals (Murphy, Monson, Oliver, & Leighton, 1987; Simon, Von Korff, Saunders, Miglioretti, van Belle, & Kessler, 2006), further consideration could be given to the extent to which risk factors might be particularly high for males with endogenous depression. In addition to health risk behaviors, cognitive and affective patterns associated with depression may have an adverse effect on cardiovascular functioning (Pratt, Ford, Crum, Armenian, Gallo, & Eaton, 1996). A further potential line for investigation might consider the ways in which endogenous depression and related stressors might have a direct physiological impact on cardiovascular functioning (Selye, 1956). Such research holds the potential of directing efforts at IHD prevention to depressed patients through modifications in health-related behaviors and cognitions.

Several limitations of the present study should be noted. The associations found do not necessarily entail that endogenous depression has a causal role in the etiology of IHD. An alternate explanation of the findings is that the provision of health care for men with endogenous depression is less adequate than it is for the general population (Lawrence, Holman, Jablensky, & Hobbs, 2003). Differential levels of care could possibly arise because treatment focuses heavily on the symptoms of depression, rather than physical illnesses. In addition, among severely depressed patients, physical symptoms may also be misattributed to depression (Mykletun, Bjerkeset, Øverland, Prince, Dewey, & Stewart, 2009). A further limitation to the present study arises from regional differences in IHD death rates. Because the sample of depressed patients in the present study was drawn from the South of England, where IHD death rates are below the national average (Selye, 1956), the use of national IHD death rates may slightly overestimate the expected IHD death rate in the non-depressed population. To the extent that the predicted IHD death rate is over-estimated, the present study might slightly underestimate the association between clinical depression and IHD. National IHD death rates were nonetheless used because they provided a more comprehensive view of trends in IHD death by age and sex over the past 50 years. A third major limitation to the present study arises from the lack of information concerning participants' health status prior to death. We do not know whether depressed patients were more likely to have suffered from IHD attacks, or whether they were simply less likely to survive and recover from IHD. As noted earlier, the data do not allow us to control for the effects of other health behaviors and conditions that are often confounded with depression.

As noted the dichotomy that existed in 1960 between endogenous and reactive depression no longer has support nevertheless it is particularly interesting that these results do provide support for a dichotomy.

5. Conclusion

In summary, the results of the present study are consistent with those of other investigations that have found an increased rate of premature IHD death among depressed individuals. The present study shows that the relationship between depression and increased risk of premature IHD death holds when the assessment of depression is based on a formal and rigorous psychiatric assessment, and when IHD mortality rates are established over an extended follow-up period. The results of the present study further suggest that the associations between clinical depression and premature IHD mortality should be considered in the context of sex and type of depression. Men with endogenous depression appear to be at particularly elevated risk for premature death from IHD, and may be in particular need of clinical interventions to assess and modify other IHD risk factors.

Acknowledgements

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