

Suicide Risk in Primary Care Patients With Major Physical Diseases

A Case-Control Study

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Context: Most previous studies have examined suicide risk in relation to a single physical disease.

Objectives: To estimate relative risk across a range of physical diseases, to assess the confounding effect of clinical depression and effect modification by sex and age, and to examine physical illness multimorbidity.

Design: Nested case-control study.

Setting: Family practices (n=593) registered with the General Practice Research Database from January 1, 2001, through December 31, 2008. The case-control data were drawn from approximately 10.6 million complete patient records, pertaining to approximately 8% of the total population of the United Kingdom, with complete linkage to national mortality records.

Participants: A total of 873 adult suicide cases and 17 460 living controls matched on age and sex were studied. The reference group for relative risk estimation consisted of people without any of the specific physical illnesses examined.

Main Outcome Measures: Suicide and open verdicts.

Results: Among all patients, coronary heart disease, stroke, chronic obstructive pulmonary disease, and osteoporosis were linked with elevated suicide risk, and, with the exception of osteoporosis, the increase was explained by clinical depression. The only significantly elevated risk in men was with osteoporosis. Female effect sizes were greater, with 2- or 3-fold higher risk found among women diagnosed as having cancer, coronary heart disease, stroke, chronic obstructive pulmonary disease, and osteoporosis. In women with cancer and coronary heart disease, a significant elevation persisted after adjustment for depression. Overall, heightened risk was confined to physically ill women younger than 50 years and to older women with multiple physical diseases.

Conclusions: Our findings indicate that clinical depression is a strong confounder of increased suicide risk among physically ill people. They also demonstrate an independent elevation in risk linked with certain diagnoses, particularly among women. Health care professionals working across all medical specialties should be vigilant for signs of undetected psychological symptoms.

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PHYSICALLY ILL PEOPLE ARE more likely to have poor mental health and vice versa,¹ and suicide occurs more frequently with the coexistence of psychiatric and physical illnesses.² The relevant literature is dominated by investigations of a single physical illness, with higher risk indicated with asthma,³ cancer,^{4,5} coronary heart disease,⁶ diabetes mellitus,⁷ epilepsy,^{8,9} and stroke.¹⁰ Few studies¹¹⁻¹³ have compared effects among different physical illnesses in the same cohort. The range of conditions that confer higher risk may be broader than the current literature suggests, and the underlying reasons for this

association are not fully understood. In particular, a greater understanding of the confounding role of clinical depression is needed. The association between physical illness and suicide is a major clinical and public health issue for several reasons. First, these patients usually have regular health service contact, which offers more opportunities for monitoring and intervention. Second, clinical depression is the key risk factor for suicide¹⁴ and is considerably more common in physically ill people. It can be treated effectively in this population¹⁵ and thereby reduce risk.¹⁶ Third, the proportion of suicides known to be associated with physical illness is considerable for indi-

viduals 50 years or older,¹⁷ which implies a significant population impact.

Conducting such research requires large cohorts because of the rarity of suicide. We used the United Kingdom's General Practice Research Database (GPRD),^{18,19} which has been used to investigate mortality^{11,20} and depression.^{21,22} Its potential has been further enhanced by recent implementation of complete linkage to national mortality records. We addressed the following research questions: (1) How does relative risk of suicide vary among different types of major physical illness among all registered primary care patients? (2) To what degree does clinical depression detected by health care services explain elevated risk? (3) Is relative risk modified by sex and age? (4) Does risk increase with increasing levels of physical illness multimorbidity?

We hypothesized higher risk across all 11 physical diseases examined. We expected depression to largely explain any elevated risks observed and that risk would be greatest in those with multiple illnesses.¹³ We also assessed age- and sex-specific effects because most previous studies^{12,13,23-25} have investigated older people. Evidence is lacking for effects at younger age²⁶ and by sex.

METHODS

DATA SETS AND OUTCOME ASCERTAINMENT

The case-control study was constructed using the GPRD,^{18,19} the world's largest population-based, longitudinal, primary care database. Before our study data set was created, the Independent Scientific Advisory Committee of the GPRD granted ethics approval. Consent from individual patients is not required for GPRD-based studies. Although participating practices were not randomly sampled, the database provides a broadly representative sample of all people registered with a family practice, which applies to virtually every resident of the United Kingdom. The September 2010 version we analyzed contained approximately 10.6 million complete patient records from 593 family practices, including approximately 8% of the total population. It routinely records all primary care consultations for registered patients, with comprehensive and detailed clinical coding for symptoms, diagnoses, treatment (including prescribed medication), and referral to other forms of National Health Service care and to other health care providers. During 2008, complete prospective and historic linkage to national mortality registration systems was implemented via the Office for National Statistics, England and Wales, and the General Register Offices for Scotland and for Northern Ireland.

We included adult suicides if the individual died from January 1, 2001, through December 31, 2008, and had at least 2 full years of "up-to-standard" GPRD clinical data. These quality criteria were also applied in selecting living controls. In the United Kingdom, most unnatural deaths of undetermined cause (or open verdicts) among adults are considered likely to be suicides.²⁷ To reduce false-negative misclassification²⁸ and in line with standard practice for conducting epidemiologic studies of suicide in the United Kingdom, our case definition included these open verdicts. We used the following ICD-10 codes: X60-84 and Y10-34²⁹ (excluding Y33.9; ie, deaths with adjourned inquests that are mostly deemed subsequently to be homicides).³⁰ By this definition, the male suicide rate in the United Kingdom in 2009 was 17.5 per 100 000 population and the female rate was 5.2 per 100 000 population.³¹

PHYSICAL DISEASES AND CLINICAL DEPRESSION

We examined major physical illnesses that either place a heavy burden on primary care services in the United Kingdom³² or are indicated in the literature as being likely correlates of suicidal behavior or clinical depression. We delineated them using the Read/OXMIS codes that capture the complete clinical record of each GPRD patient.³³ Read/OXMIS is a hierarchical coding system widely used in primary care in the United Kingdom. For major disease groups, the first digit denotes the chapter heading, with subheadings giving progressively more detail (eg, G, circulatory system diseases; G3, ischemic heart disease; G30, acute myocardial infarction; and G300, acute anterolateral myocardial infarction). Recent validation showed that ICD-9 codes for identifying multiple physical diseases can be readily translated for examination in the GPRD.³⁴ Two of us (E.K. and T.D.) have previously examined the effect of national schemes to incentivize general practitioners to improve their quality of care.³⁵ We conducted an extensive consensus-development process with experienced academic general practitioners to identify valid codes denoting major illnesses in the GPRD and other national routinely collected data sets. We then applied their coding ranges. The conditions that we examined were cancer, coronary heart disease, hypertension, stroke, diabetes, asthma, chronic obstructive pulmonary disease (COPD), osteoarthritis, osteoporosis, back pain, and epilepsy (**Table 1** and **Figure 1**).

In addition, Doran and colleagues³⁵ had identified coding ranges for clinical depression. We used these to delineate previous or current episodes recorded in the patient's clinical record, according to diagnoses made before suicide by general practitioners or specialist mental health services. To achieve comprehensive adjustment for depression as a confounder, patients with a history of depression but who were not known to be depressed at the time of their suicide were classified as having depression unless their record clearly indicated that their condition had remitted. For controls, it was necessary for all physical illnesses and clinical depression to have been coded in the GPRD before the matched case's date of death. The detailed lists of Read/OXMIS codes used are available on request from the corresponding author.

STUDY DESIGN AND STATISTICAL ANALYSIS

The analyses were conducted using Stata statistical software (StataCorp). The 873 suicides in our case-control study were matched to 17 460 living controls by sex, age (in years), and date of death. Twenty controls were selected from the age-, sex-, and time-specific risk set of each case to maximize power for precise effect estimation with physical illnesses of low prevalence.³⁶ We calculated prevalence among cases and controls separately and generated conditional logistic regression models to estimate relative risks as exposure odds ratios (ORs) across both sexes. These models were adjusted inherently for sex and age in the matched design. We then fitted sex interaction terms and formally tested their significance. The incidence density sampling in the nested case-control design meant that the ORs were interpretable as hazard ratios (relative risks), as would be derived from survival analysis of the entire cohort.³⁷ To make our estimates comparable among specific physical illnesses, we applied a generic reference category (ie, patients with none of the 11 assessed physical illnesses). This was a heterogeneous group. In the United Kingdom, virtually the entire population is registered with a family practice, meaning that some of these people will have been completely well, whereas others will have had conditions that we did not examine. Younger registered patients are more likely to have been fit and well than older ones, but age-matching ensured that this did not confound our estimates.

Table 1. Relative Risk of Suicide in Patients With Specific Physical Illnesses: Main Effects^a

Physical Illnesses	No. (%)		Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) ^b	Median Age, y ^c
	Cases (n = 873)	Controls (n = 17 460)			
None of the illnesses	535 (61.3)	11 002 (63.0)	1.00 [Reference]	1.00 [Reference]	43
Any of the illnesses	338 (38.7)	6458 (37.0)	1.10 (0.94-1.29)	0.89 (0.75-1.04)	62
Specific illnesses					
Cancer	30 (3.4)	561 (3.2)	1.14 (0.77-1.70)	0.96 (0.64-1.45)	70
Coronary heart disease	71 (8.1)	1035 (5.9)	1.53 (1.14-2.04)	1.09 (0.81-1.46)	74
Hypertension	132 (15.1)	2828 (16.2)	0.97 (0.77-1.21)	0.80 (0.64-1.01)	70
Stroke	34 (3.9)	488 (2.8)	1.54 (1.04-2.28)	1.09 (0.73-1.63)	79
Diabetes mellitus	47 (5.4)	845 (4.8)	1.18 (0.85-1.62)	0.90 (0.65-1.26)	67
Asthma	85 (9.7)	1623 (9.3)	1.09 (0.86-1.38)	0.84 (0.66-1.08)	46
COPD	27 (3.1)	329 (1.9)	1.80 (1.18-2.76)	1.29 (0.83-2.00)	66
Osteoarthritis	76 (8.7)	1688 (9.7)	0.94 (0.72-1.24)	0.68 (0.51-0.91)	76
Osteoporosis	23 (2.6)	222 (1.3)	2.33 (1.46-3.72)	1.62 (0.99-2.63)	77
Back pain	31 (3.6)	548 (3.1)	1.18 (0.81-1.72)	0.85 (0.58-1.25)	48
Epilepsy	10 (1.1)	156 (0.9)	1.33 (0.70-2.55)	1.10 (0.56-2.14)	57.5

Abbreviation: COPD, chronic obstructive pulmonary disease.

^aAll odds ratios listed in this table are adjusted for sex and age by the case-control matching. Statistically significant ($P < .05$) odds ratios are highlighted in bold.

^bMultivariate adjustment for clinical depression.

^cMedian age of cases (and age-matched controls) when case died.

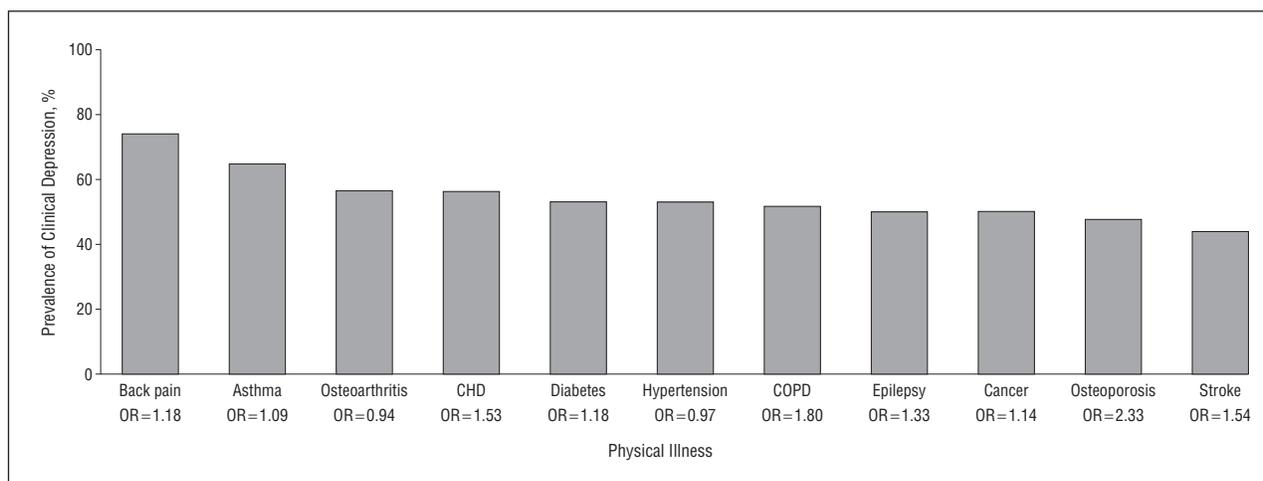


Figure 1. Prevalence of depression among suicide cases by specific physical illness. The odds ratios (ORs) in all patients diagnosed as having specific physical illnesses (as listed in Table 1) are shown for comparison (Pearson coefficient for the correlation between depression prevalence and the observed OR: -0.42 , $P = .20$). CHD indicates coronary heart disease; COPD, chronic obstructive pulmonary disease.

RESULTS

RELATIVE RISK AMONG ALL PATIENTS

We observed 658 male suicide cases matched to 13 160 controls and 215 female suicide cases matched to 4300 controls (aged 17-98 years). Three-quarters (650 [74.5%] of 873) of all cases were definite suicides as opposed to open verdicts, with comparable distributions by verdict type according to sex (men, 75.5%; women, 71.2%; $\chi^2_1 = 1.6$; $P = .20$) and age (<50 years, 72.9%; ≥ 50 years, 76.1%; $\chi^2_1 = 1.2$; $P = .27$). A total of 38.7% of all cases and 37.0% of controls had been diagnosed as having any of the 11 physical illnesses assessed, and there was no evidence of higher suicide risk per se in this group (Table 1). For each specific physical illness, the OR point estimate was greater than unity, except for osteoarthritis and hypertension. Pa-

tients with coronary heart disease, stroke, COPD, and osteoporosis had significantly elevated risk compared with the reference group without any of the examined illnesses, but in multivariate models, these effects were largely explained by clinical depression. The highest relative risk observed was with osteoporosis, with the elevation in risk persisting after adjustment for depression. For osteoarthritis, adjustment revealed a statistically significant apparent protective effect. The median age at suicide ranged from 46 years with asthma to 77 years with osteoporosis.

PREVALENCE OF CLINICAL DEPRESSION

Prevalence of depression among all suicide cases with any of the 11 physical illnesses was 57.7% vs 47.9% in cases without such illnesses ($\chi^2_1 = 8.0$; $P = .005$). It was also higher in male cases with a physical illness vs those without

Table 2. Relative Risk of Suicide in Patients With Specific Physical Illnesses: Evidence of Effect Modification by Sex^a

Physical Illnesses	No. (%)		Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI) ^b	Median Age, y ^c
	Cases (n = 873)	Controls (n = 17 460)			
Any of the illnesses					
Men	227/658 (34.5)	4504/13 160 (34.2)	1.02 (0.84-1.23)	0.82 (0.68-1.00)^d	61
Women	111/215 (51.6)	1954/4300 (45.4)	1.39 (1.01-1.90)	1.10 (0.80-1.52)	64
χ^2_{int}			2.8	2.2	
P value			.10	.14	
Cancer					
Men	12/658 (1.8)	360/13 160 (2.7)	0.66 (0.36-1.21)	0.56 (0.30-1.04)	76.5
Women	18/215 (8.4)	201/4300 (4.7)	2.23 (1.28-3.86)	1.85 (1.04-3.26)	69.5
χ^2_{int}			8.5	7.6	
P value			.004	.006	
Coronary heart disease					
Men	47/658 (7.1)	817/13 160 (6.2)	1.19 (0.84-1.68)	0.87 (0.61-1.24)	74
Women	24/215 (11.2)	218/4300 (5.1)	3.10 (1.81-5.29)	2.04 (1.18-3.55)	74
χ^2_{int}			8.7	6.3	
P value			.003	.01	
COPD					
Men	17/658 (2.6)	249/13 160 (1.9)	1.41 (0.83-2.39)	1.09 (0.63-1.88)	66
Women	10/215 (4.7)	80/4300 (1.9)	3.23 (1.57-6.66)	1.90 (0.89-4.06)	63
χ^2_{int}			3.3	1.3	
P value			.07	.26	

Abbreviation: COPD, chronic obstructive pulmonary disease.

^aEffects with a statistically significant ($P < .05$) or borderline significant ($P > .05$, $P < .10$) sex interaction; all Table 1 main effects were refitted with a sex interaction term added to each conditional logistic regression model. All statistically significant sex-specific odds ratios are highlighted in bold.

^bMultivariate adjustment for clinical depression.

^cMedian age of cases (and age-matched controls) when case died.

^dThis effect was statistically significant (ie, upper confidence limit = 0.995).

^eInteraction test.

(53.3% vs 43.2%; $\chi^2_{\text{int}} = 6.2$; $P = .01$), whereas among female cases, no difference in prevalence was found between these 2 groups (66.7% with physical illness vs 67.3% without; $\chi^2 = 0.01$; $P = .92$). Prevalence among all living controls with physical illnesses was 19.9% vs 12.6% in those with no physical illnesses ($\chi^2_{\text{int}} = 164.8$; $P < .001$). Figure 1 shows the variation in prevalence among suicides across the specific physical illnesses examined. Prevalence was approximately two-thirds or greater in cases with asthma (64.7%) and back pain (74.2%) and was lower than half in those with osteoporosis (47.8%) and stroke (44.1%). Across the specific illnesses, we tested for correlation between the OR point estimate and prevalence of depression in each illness (Table 1). The Pearson coefficient was -0.42 but was nonsignificant ($P = .20$).

SEX- AND AGE-SPECIFIC EFFECTS

The median age of all female suicide cases (54 years) was significantly greater than that of male suicide cases (48 years) (Wilcoxon rank-sum test, $P < .001$), and the prevalence of physical illness was greater in women (Table 2). Evidence of effect modification by sex is also given in Table 2. Women with any of the physical illnesses assessed had significantly elevated suicide risk, with no effect at all evident in men, although the sex difference did not reach significance ($P = .10$). Almost without exception, relative risks were greater in women than men across the specific illnesses. Highly significant sex differences

were seen among patients diagnosed as having cancer and coronary heart disease. For these 2 conditions, the elevated risk among women was independent of clinical depression, with an approximate doubling of risk indicated in the multivariate models. There was a particularly strong sex interaction with cancer; a more than 2-fold significant increase in risk was seen among these women, but there was no evidence of an effect in men. The OR in men diagnosed as having cancer was lower than unity but with no significant evidence of a protective effect ($\chi^2_{\text{int}} = 1.8$; $P = .18$). For COPD, a highly significant 3-fold elevation in risk was seen in women, although the sex interaction term was marginally nonsignificant. These sex-specific analyses revealed considerably greater relative risks in women (than men) for cancer, coronary heart disease, and COPD (effects that were hidden in the main effects presented in Table 1).

Two additional sex-specific effects, with nonsignificant interaction terms and hence not listed in Table 2, are also noteworthy. First, for osteoporosis, a comparable increase in risk was indicated in both sexes (men: 8 cases; OR, 2.72; 95% CI, 1.27-5.82; women: 15 cases; OR, 2.44; 95% CI, 1.32-4.51). Osteoporosis was the only specific physical illness examined that was associated with a significantly elevated risk in men. Second, for stroke, although the sex interaction term was nonsignificant ($\chi^2_{\text{int}} = 1.0$; $P = .32$), a more than doubled risk was indicated in these women (10 cases; OR, 2.14; 95% CI, 1.03-4.45), whereas in men, the increase was nonsignificant (24 cases; OR, 1.38; 95% CI, 0.87-2.19).

Table 3. Sensitivity Analysis Comparing Significant Sex-Specific Odds Ratios With and Without Open Verdicts Included in the Suicide Case Definition^a

Physical Illnesses	Odds Ratio (95% CI)	
	Suicide and Open Verdicts	Suicide Verdicts Only
Cancer in women	2.23 (1.28-3.86)	2.15 (1.15-4.03)
Coronary heart disease in women	3.10 (1.81-5.29)	2.09 (1.05-4.16)
Stroke in women	2.14 (1.03-4.45)	1.77 (0.70-4.46)
COPD in women	3.23 (1.57-6.66)	2.78 (1.11-6.96)
Osteoporosis		
Men	2.72 (1.27-5.82)	2.48 (1.04-5.95)
Women	2.44 (1.32-4.51)	1.90 (0.88-4.11)

Abbreviation: COPD, chronic obstructive pulmonary disease.
^aAll statistically significant sex-specific odds ratios are highlighted in bold.

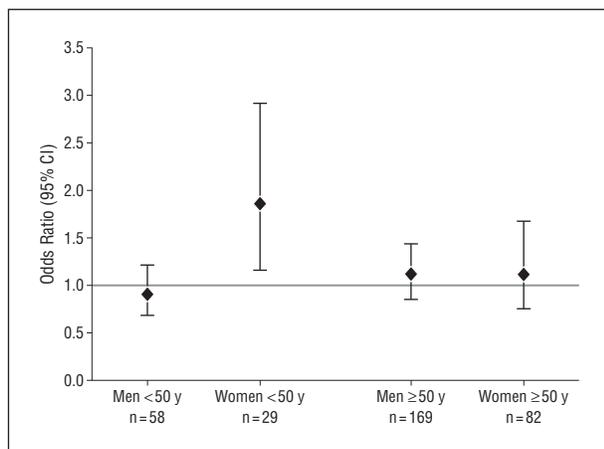


Figure 2. Sex-specific relative risk of suicide in patients diagnosed as having any of the physical illnesses stratified by age ($\chi^2 = 6.5$, $P = .01$, for sex interaction at younger than 50 years).

For the 5 female and 1 male disease-specific ORs that were significantly elevated, we performed a sensitivity analysis assessing the impact of including open verdicts in the suicide case definition (**Table 3**). With only definite suicide cases examined, the effect sizes were attenuated somewhat, and 2 of the female-specific effects (osteoporosis and stroke) became nonsignificant, perhaps partly due to reduced power. The findings overall, however, were essentially unchanged.

We assessed the sex-specific effect for having any of the 11 physical illnesses in cases 50 years or older and those younger than 50 years (**Figure 2**). At 50 years or older, there was no evidence of a difference in risk by sex (interaction test: $\chi^2 = 0.0$; $P = .96$). However, in those younger than 50, there was an almost doubled risk in women and no increased risk for men (interaction: $\chi^2 = 6.5$; $P = .01$). The effect in women younger than 50 was partially explained by clinical depression (unadjusted OR, 1.85; 95% CI, 1.16-2.92; adjusted OR, 1.38; 95% CI, 0.86-2.22). There was a suggestion of higher prevalence of depression among the younger female suicide cases (23 of 29 [79.3%]) compared with those 50 years or older (51 of 82 [62.2%]), although this difference was nonsignificant ($\chi^2 = 2.8$; $P = .09$).

We fitted age interaction terms (<50 vs ≥ 50 years) against each specific physical illness for both sexes combined because of small cell values for some of the sex- and age-specific ORs. With COPD, there was a much stronger effect at younger age (<50 years: 4 cases; OR, 16.11; 95% CI, 4.32-60.03; ≥ 50 years: 23 cases; OR, 1.55; 95% CI, 0.97-2.47; age interaction: $\chi^2 = 10.8$; $P = .001$), although this result should be viewed cautiously because of the small number of younger suicide cases. There was no evidence of an age difference in the effect linked with osteoporosis ($P = .17$).

PHYSICAL ILLNESS MULTIMORBIDITY

Overall, there was no evidence of increasing risk linked with increasing multimorbidity, and this was also true for men only (**Table 4**). However, risk in women with 3 or more physical illnesses was more than twice as high as in those without any of the examined conditions, with strong evidence of a linear trend. These female cases generally died at an older age (median, 77 years), and the higher risk was only partially explained by clinical depression (adjusted OR, 1.53; 95% CI, 0.90-2.59). There was a significant sex interaction among patients with 3 or more physical diseases ($\chi^2 = 6.5$; $P = .01$). Comparing these results with those shown in Figure 2, we expected to find a more marked effect of multimorbidity in younger women. However, this was hard to assess because there were just 4 female cases younger than 50 years with 2 physical illnesses and 3 younger cases with 3 or more conditions. Nonetheless, the point estimate was large for younger women with 3 or more illnesses (OR, 9.51; 95% CI, 2.32-39.01). This effect was highly significant ($\chi^2 = 9.8$; $P = .002$) but should be viewed cautiously because of its imprecision. In men, there was no evidence of higher risk with multimorbidity at younger than 50 years or 50 years or older.

DETAILED INVESTIGATION OF ELEVATED RISK IN WOMEN WITH CANCER

We examined the records to identify reasons for the strong sex interaction. The 18 female suicide cases died at a younger age than did the 12 male cases (median, 69.5 vs 76.5 in men) but not significantly so (Wilcoxon rank-sum test, $P = .21$). Also, a longer time elapsed between first diagnosis of cancer and suicide in the female cases (median, 5.99 years in women vs 1.52 years in men), but again the difference was not significant ($P = .15$). Half of the female suicide cases with cancer (9 of 18) had experienced malignant neoplasm of the breast. Suicide risk was approximately doubled in this subgroup (OR, 2.06; 95% CI, 0.99-4.29) as it was in all women with cancer.

COMMENT

SUMMARY OF FINDINGS

Among all primary care patients, we found significantly higher suicide risk with coronary heart disease, stroke, COPD, and osteoporosis. Female effect sizes were gen-

Table 4. Relative Risk of Suicide by Increasing Level of Physical Illness Multimorbidity^a

No. of Physical Illnesses	No. (%)		Odds Ratio (95% CI)	Median Age, y ^b
	Cases (n = 873)	Controls (n = 17 460)		
All people				
0	535 (61.3)	11 002 (63.0)	1.00 [Reference]	43
1	202 (23.1)	3916 (22.4)	1.09 (0.91-1.29)	55
2	80 (9.2)	1592 (9.1)	1.08 (0.83-1.41)	70.5
≥3	56 (6.4)	950 (5.4)	1.29 (0.94-1.78)	77
χ^2_{c}			2.2	
P value			.14	
Men				
0	431/658 (65.5)	8656/13 160 (65.8)	1.00 [Reference]	43
1	144/658 (21.9)	2787/13 160 (21.2)	1.04 (0.84-1.27)	55
2	53/658 (8.1)	1087/13 160 (8.3)	0.97 (0.71-1.34)	70
≥3	30/658 (4.6)	630/13 160 (4.8)	0.95 (0.62-1.44)	77.5
χ^2_{c}			0	
P value			.89	
Women				
0	104/215 (48.4)	2346/4300 (54.6)	1.00 [Reference]	46
1	58/215 (27.0)	1129/4300 (26.3)	1.27 (0.89-1.79)	53.5
2	27/215 (12.6)	505/4300 (11.7)	1.42 (0.88-2.30)	73
≥3	26/215 (12.1)	320/4300 (7.4)	2.27 (1.35-3.84)	77
χ^2_{c}			8.6	
P value			.003	

^aMultimorbidity is measured as the number of physical illnesses from the list of 11 illnesses examined in this study, not the total number of illnesses recorded in the General Practice Research Database.

^bMedian age of cases (and age-matched controls) when case died.

^cLinear trend test.

erally stronger than their equivalent male effects, and the only significantly elevated risk found in men was with osteoporosis. Significantly increased risk was seen in women who had any of the physical illnesses examined, and a 2- or 3-fold higher risk was indicated in women with cancer, coronary heart disease, stroke, COPD, and osteoporosis. Elevated risk in women with cancer or coronary heart disease was independent of clinical depression. Risk was greater in younger, physically ill women per se and in older women with multimorbidity.

COMPARISON WITH EXISTING EVIDENCE AND INTERPRETATION

A few case-control studies have previously been reported. For example, a smaller study,¹¹ conducted from 1991 through 1993 using the GPRD, found no evidence of higher risk with a range of physical diseases. It lacked systematic linkage to national mortality data and thus may have been prone to ascertainment bias and low power. A second small case-control study,¹² conducted among elderly people in Gothenburg, Sweden, reported that serious physical illness and a greater total burden of illness predicted higher risk, with these effects restricted to men. With just 85 cases it also lacked power, and less than two-thirds of those eligible for sampling as controls consented to participate. By contrast, we found greater female effect sizes.

Our failure to observe elevated risk in physically ill men requires explanation, especially given that rates are high for elderly men in many Western countries.³⁸ A study³⁹ of the US National Health Interview Survey linked

with the National Death Index reported that chronic physical illness did not predict suicide independent of functional limitation. Thus, associated disability rather than illness per se could be the key determinant in men. Our findings suggest that increased risk may be restricted to certain groups; for example, younger, physically ill women, older women with multiple illnesses, and those with only some of the 11 specific diseases examined. Insufficient statistical power might explain why we failed to find more significant effects across the full range of illnesses examined, in both sexes, and across the adult age range. However, this seems unlikely because our study was much better powered to detect male effects than female ones (there were >3 times more male suicides) and because some of the illnesses indicating no association were in fact adequately powered to detect modest effect sizes. This was so for asthma, diabetes, hypertension, and osteoarthritis, for example. A more likely explanation lies with the intrinsic nature of this primary care population. Stronger effects across a broader range of illnesses and in all demographic subgroups might be seen by investigating a cohort treated for these illnesses in secondary care.

Scandinavian registry studies have shown higher risk in patients diagnosed as having myocardial infarction,⁶ stroke,¹⁰ and epilepsy.^{8,9} We did not find an association with epilepsy, perhaps due to low power, because we observed only 10 suicide cases with this diagnosis. National registry studies conducted in Taiwan showed higher risk with asthma³ and diabetes,⁷ but these findings may not generalize to Western nations, and the asthma study was restricted to young people. We found a 2- to 3-fold

elevated risk with COPD in women and osteoporosis in both sexes. To our knowledge, these associations have not been reported previously, although recent reviews have indicated higher rates of depression in these 2 groups.^{40,41} The higher risk in men and women with osteoporosis, a novel finding, may be linked with fracture and trauma, although we could find no evidence of such an association in the existing literature. As with most of the other conditions we examined, elevated risk in patients with osteoporosis may be linked with unhealthy lifestyles, such as smoking⁴² and heavy alcohol use,⁴³ which are also established risk factors for suicide.^{44,45}

Previous population-based studies have shown higher risk after diagnosis with cancer, with conflicting evidence of a sex difference. For example, relative risk was higher for women than men during the 1950s and 1960s in the Finnish Cancer Registry⁴ and vice versa in the Swedish Cancer-Environment Register during the 1960s and 1970s.⁵ Recent reports from Sweden⁴⁶ and Italy⁴⁷ indicate decreasing risk associated with cancer, perhaps due to improved treatment outcome and better communication of diagnosis.⁴⁷ Suicide is especially likely soon after diagnosis,^{5,48} although long-term follow-up of almost 724 000 women in the United States and Scandinavia showed that elevated risk persists for up to 2 to 3 decades after breast cancer diagnosis,^{49,50} the most common cancer in women. Increased levels of psychological distress among breast cancer survivors may be due to the adverse effects of mastectomy.^{51,52} This procedure had occurred in only 3 of the female suicide cases we observed, and so we could not estimate relative risk specifically in these women. Overall, we did not see a higher risk specific to neoplasm of the breast vs other cancers in women.

STRENGTHS AND LIMITATIONS

The GPRD uniquely provides a large, detailed, and nationally representative computerized cohort of primary care-treated mental and physical illness, with complete linkage and follow-up of cause-specific mortality. Investigation of rare exposures and events is possible, and biases that commonly flaw epidemiologic studies are minimized. For example, information bias is reduced because the data are collected prospectively, irrespective of subsequent outcome. National registers in Denmark and Sweden have collected details of all hospital admissions during several decades, but we could investigate milder forms of physical illness among people not hospitalized. We could also make a more comprehensive assessment of the confounding role of clinical depression, as detected by all national public health care services in both primary and secondary care settings.

Selection into primary care was an unlikely source of major bias because almost all residents of the United Kingdom are registered with a general practitioner soon after their birth. When people move and register with a new practice, their complete primary health care record is transferred automatically. Thus, the GPRD is a representative community sample. Female patients, especially those who are mentally ill, may see their general practitioner more often than their male counterparts, giving

physicians more opportunities to diagnose physical illnesses. This bias may pertain to conditions such as back pain, osteoporosis, and hypertension because they may not require urgent medical attention. However, it is unlikely to have affected our assessments of the other 8 physical illnesses. These are conditions that need active clinical care, which in the United Kingdom is mostly provided through primary care. Patients' general practitioners are formally notified of diagnoses made by physicians in public or private hospitals, and this information is thereby captured in the GPRD. Thus, for most of the illnesses we examined, biased selection into primary care is an unlikely explanation for the excess risk we found in female patients.

The main limitation of our study was potential misclassification of exposure status, which occurred for 4 main reasons. First, our generic reference group consisted of patients without any of the assessed physical illnesses. Patients in this group may have had other medical conditions that we did not examine. However, we adopted a pragmatic approach that enabled direct comparison of effects across the specific illnesses. Delineation of GPRD patients with no major physical illnesses of any sort would be an infeasible task with such a large data set containing so much detailed and complex coding. Second, our adjustments for clinical depression were not fully comprehensive because we could not assess depression among people who did not seek treatment or that was not detected by health care services. We attempted additional adjustments for all Axis I disorders, including anxiety disorders and substance dependence. However, we were not completely confident of identifying all episodes of these disorders in the Read/OXMIS coding, and so we adjusted for clinical depression only. Third, because of logistical constraints in examining multiple diseases, we did not use GPRD medication data. In defining clinical depression, we opted not to use antidepressant medication data because of historic concerns about subtherapeutic dosage and prescription for indications other than depression in primary care in the United Kingdom.^{53,54} We anticipate that not including medication in defining the assessed conditions may have attenuated some effect estimates and would therefore not have generated false-positive results.⁵⁵ Finally, although the clinical records of each GPRD practice can be assumed to be complete from when the practice was computerized, for the precomputerization era, historic coding of physical diseases and depression was somewhat incomplete.

Examining a primary health care data set that includes milder illness forms might be viewed as a strength, but it could also hinder interpretation. Standardized measures of illness severity are not recorded in the GPRD, and the Read/OXMIS systems do not classify this in a structured manner. Attempts have been made to measure severity by proxy using medication dosage and duration and by number and length of hospitalizations, but we could not feasibly conduct such detailed examinations across multiple illnesses. Validation of these proxies is also unusual. Thus, medication-based severity stratification has been validated for COPD,⁵⁶ for example, but not for most of the other physical illnesses we examined. We, therefore, did not attempt to assess severity for

each specific illness, but we have shown a linear relationship of increasing risk by increasing multimorbidity among women. This factor could be viewed as a proxy for severity, although not all severely ill patients will have experienced more than 1 major physical disease.

One final limitation was the lack of sociodemographic data held by the GPRD. Risk factors, such as marital status, social class, unemployment, and living alone, are not recorded during routine patient consultations. We, therefore, could not adjust for these important confounders.

To our knowledge, this is the first large population-based study to examine suicide risk in a broad range of physical diseases with systematic and complete linkage to national mortality data. Our findings show that health care professionals working across all medical specialties should be vigilant for signs of undetected psychological symptoms,^{2,37} especially when treating women diagnosed as having cancer, coronary heart disease, COPD, osteoporosis, or stroke. Previous or current clinical depression did not explain elevated risk seen in women with cancer and coronary heart disease, and it only partially explained higher risk seen in younger, physically ill women and those with multiple diseases. For these groups of women, our results challenge the notion that physical illness and associated disability lead to depression, which leads to suicide. It could be that younger women feel threatened by serious physical disease, particularly those that are widely known to be the most common causes of premature death. The specific mechanisms involved are likely to vary greatly according to the nature of the physical illness being considered, and further research is therefore needed to understand the causal pathways. Training for a wider range of health care professionals in suicide risk management and reduction may be beneficial. Addressing this need could greatly improve patients' quality of life by tackling their psychological distress, as well as potentially reducing population-level suicide rates.

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