Depression as a risk factor
for total mortality in the community:
a meta-analysis

by

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Abstract

Aim: There is growing evidence that depression is associated with an increased mortality risk, but results from studies are ambiguous. To investigate whether depression leads to increased mortality, we reviewed the literature on depression and total mortality in the community. We also performed statistical pooling.

Methods: We searched Medline and Psychinfo for relevant articles published between January 1966 and December 2000 and checked the references in the articles found in our search. We used the following inclusion criteria: published in English, Dutch or German language; prospective community based studies describing at least total mortality; the presence of a control group and the use of DSM-criteria or criteria resembling DSM in a reasonable way or by a validated and reliable depression questionnaire in the diagnosis of depression.

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Results: *Twenty-four studies were included in our review. Of the 19 studies reporting data on males and females together, nine reported a significant positive association. The majority of studies showed a positive non-significant association between depression and mortality. No significant negative associations were reported. Overall the summary estimated relative risk was 1.56 (1.31-1.85).*

Conclusions: *Our results support the hypothesis of depression being a risk factor for increased total mortality.*

Keywords: *depressive disorder, mortality, meta-analysis*

Introduction

A lot of research has been done on mortality following depression. In 1999 Wulsin(1) reviewed all mortality studies (N=57) published from 1966 to 1996.

Fifty-one percent of the studies showed a positive association between depression and mortality, twenty-three percent showed a negative association and fifteen percent showed mixed results. These contradictory findings may be explained by important differences in the definition of depression, the study population, the length of follow-up, the causes of death and additional characteristics the authors controlled for. This variety makes it difficult to compare and summarize the results of the different studies. For this reason, most reviews written on this subject include a fraction of the existing studies only, based on certain inclusion criteria (2-4). In this meta-analysis we focus on depression and mortality in the community and we include cohort studies that describe the effect of depression on subsequent total mortality.

Methods

Literature search

We searched the Medline and Psychinfo databases for data from January 1966 until December 2000, crossing [depress*] with [mortality or dead or death or died]. This resulted in over 10,000 studies of which we selected the ones that met the following criteria: published in English, Dutch or German language; prospective epidemiological studies; community based studies (excluding studies starting from a selected group of depressed patients, e.g. patients recruited in secondary or

tertiary care settings or including patients with an additional disease only); describing general mortality (not cause specific only); presence of a control group (not compared with figures from the general population) and the use of DSM-criteria or criteria resembling DSM in a reasonable way or by a validated and reliable depression questionnaire for the diagnosis of depression. In addition we checked the references in the selected articles to find other relevant publications.

Selection and data collection

The selection of studies was initially based on reading the abstract. If the abstract was unclear, the complete article was read to make a decision about the inclusion of the article. For each study we collected the following study characteristics: number of subjects, setting of the cohort, age range, methods used to identify the presence of depression, years of follow-up, number of deceased and surviving people in both groups, crude and adjusted risk estimate, and potential confounders used in the analyses.

Analysis

We tested for the presence of publication bias by producing a funnel plot, relating sample size and relative risk of each study. Two by two tables and unadjusted relative risks were calculated on the basis of the published data. If not enough information was available in the article to complete our tables, we contacted the author for additional information. We tested the presence of homogeneity using a chi-square test for homogeneity in the total group of reports as well as in subgroups based on characteristics such as sex, depression measure, follow-up time and continent. Summary relative risk estimates for the different subgroups were based on a random effects model and calculated using the Der Simonian and Laird method of the FASTPRO version 1.7 software (5).
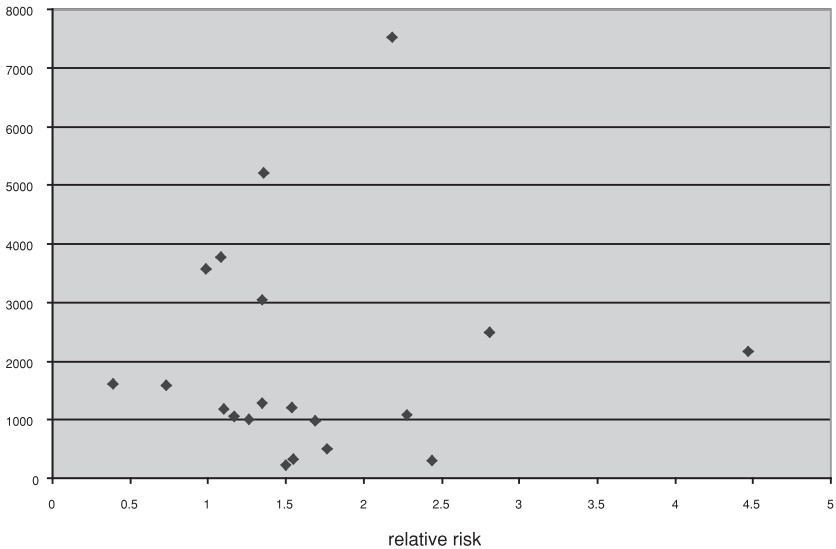
Results

Literature search and selection

By crossing [depress*] and [mortality or dead or death or died], we found over 10,000 articles in the Medline and Psychinfo search. On the basis of information given in the abstracts, we initially selected thirty-eight prospective studies. After reading the articles we rejected thirteen studies that did not match with the inclusion criteria after all. We had to exclude five more, because there were several studies on the same

study population, leaving us with twenty studies. Reference checking of the articles found in our search resulted in four more articles, bringing us to a total of twenty-four studies included in this review. The funnel plot in which measures of effect were related to sample sizes, somewhat supported the hypothesis of publication bias in studies with a total sample size below 1000 (Fig.1).

Figure 1: Cohort studies on depression and subsequent mortality: funnel plot

Basic characteristics

Table 1 shows the results of the included studies on depression and mortality.

Of the twenty-four studies, ten were conducted in the USA (6-15), 11 in Europe (16-26), two in Australia (27-28) and one in Asia (29). The smallest study included 228 subjects (28), the largest included 7518 subjects (15). In nineteen of the twenty-four studies, all subjects were over age 60 (6, 8-9, 11-13, 15-16, 18-21, 23-29), in one study they were over age 55 (22), two studies included people over age 50 (10,17), one study over age 40 (7) and one study over age 18 (14).

TABLE 1

Descriptive characteristics of prospective cohort studies on depression and mortality

Country (ref) Year of publication	Nr. of subjects in cohort	Setting	Age range (mean)	Measurement of depression Interview/diagnostic criteria	Baseline measurement (years of follow-up; mean)	Total number of deaths/number of suicides and accidents
Finland (16) 1998	971	Community sample of elderly	? (70)	DSM-III criteria	? (5)	90/No suicide data presented
Denmark (17) 1996	Total: 730 Males: 409 Females: 321	Community sample	≥ 50 ?	40-item obvious depression (OBD) subscale of the Minnesota Multiphasic Personality Inventory (MMPI)	1964 (27)	290/10 accidents or suicides in the total sample
USA (6) 1999	Total: 2489 Males: 1040 Females: 1449	Community sample of elderly Mexican Americans	≥65 ?	20-item Center for Epidemiologic Studies Depression Scale (CES-D), cut point 16	1993-1994 (2.5)	224/No death causes presented
USA (7) 1994	3560	Community sample	≥40 ? §	Diagnostic Interview Schedule (DIS)/ DSM-III criteria	1980 (9)	1194/Suicide was 1% in the total sample
USA (8) 1998	Total: 3767 Males: 1169 Females: 2598	Community sample of elderly	60-102 (Males: 67.7) (Females: 67.9)	20-item Center for Epidemiologic Studies Depression Scale (CES-D), cut point 16	1991-1993 (45 months)	561/No death causes presented

Country (ref) Year of publication	Nr. of subjects in cohort	Setting	Age range (mean)	Measurement of depression Interview/diagnostic criteria	Baseline measurement (years of follow-up; mean)	Total number of deaths/number of suicides and accidents
UK (18) 1988	1054	Community sample of elderly	≥ 65 ?	Geriatric Mental State Community version (GMS-A)/ AGECAT computer diagnostic program	1982-1983 (3)	Total: 179 Males: 83 Females: 96/ No death causes presented
Norway (19) 1996	Total: 334 Males: 78 Females: 256	Community sample of elderly	≥ 75 ?	Modified Beck rating scale/ DSM-III and DSM-III-R criteria	1984-1985 (3)	Total: 84 Males: 29 Females: 55/ No death causes presented
USA (7) 1989	Total: 1606 Males: 561 Females: 1045	Community sample of elderly	≥60 ?	Depression measure derived from the Diagnostic Interview Schedule (DIS)/ DSM-III algorithm	1982-1983 (2)	92/2 suicides in the total sample
France (20) 1999	Total: 3777 Males: 1576 Females: 2201	Community sample of elderly	≥65 (Males: 74.5) (Females: 75.5)	20-item Center for Epidemiologic Studies Depression Scale (CES-D) (French version) Males: cut point 17 Females: cut point 23	1988-1990 (5)	849/No death causes presented
USA (10) 1997	1181	Community sample	≥50 ?	DSM-III criteria	1981-1982 (13)	627/No death causes presented

Country (ref) Year of publication	Nr. of subjects in cohort	Setting	Age range (mean)	Measurement of depression Interview/diagnostic criteria	Baseline measurement (years of follow-up; mean)	Total number of deaths/number of suicides and accidents
Australia (27) 1997	1000	Community sample of elderly	≥70 ?	Canberra Interview for the Elderly (CIE)/ ICD-10 depressive episode	1990-1991 (3-6)	206/No death causes presented
Australia (28) 1991	Total: 228 Males: 87 Females: 141	Community sample of elderly	≥70 (Males: 77.4) (Females: 79.8)	Canberra version of the Geriatric Mental State Examination (GMS) in conjunction with the Mini-Mental State Examination (MMSE)/ Algorithm for diagnosis of DSM-III major Depression	1982-1983 (5-6)	94/No death causes presented
Germany (21) 1999	358	Community sample of elderly	≥85 ?	Geriatric Mental State Interview (GMS-A) /DSM-III	1990 (4 years and 8 months)	208/No death causes presented
USA (11) 1988	Total: 310 Males: 100 Females: 210	Community sample of elderly	≥65 ?	-Present State Examination 9th edition -Survey Psychiatric Assessment Schedule (SPAS) (only those questions designed to detect organic mental impairment)/ Feighner criteria for major depression	1979-1980 (4)	73/ 1 suicide in the depressed group (no causes of death presented for the non-depressed group)

Country (ref) Year of publication	Nr. of subjects in cohort	Setting	Age range (mean)	Measurement of depression Interview/diagnostic criteria	Baseline measurement (years of follow-up; mean)	Total number of deaths/number of suicides and accidents
Netherlands (22) 1999	Total: 3056 Males: 1478 Females: 1578	Community sample of elderly	55-85 (70.6)	20-item Center for Epidemiologic Studies Depression Scale (CES-D), cut point 16/ DSM-III criteria	? (4)	561/No suicides in the depressed group and 3 suicides in the non-depressed group
Finland (23) 1997	Total: 1272 Males: 518 Females: 754	Community sample of elderly	≥61 (Males: 69.8) (Females: 70.5)	DSM-III criteria	June 1984–June 1986 (6)	284/1 suicide in the depressed group and no suicide in the non-depressed group
Italy (24) 1991	Total: 1201 Males: 386 Females: 815	Community sample of elderly	70-75 ?	Revised version of Beck's Depression Inventory, cut point 23	? (3)	Total: 112 Males: 64 Females: 48/ No death causes presented
Spain (25) 1999	514	Community sample of elderly	≥65 ?	Spanish version of the Geriatric Mental State (GMS) and the History and Aetiology Schedule (HAS)/ AGECAT computer diagnostic program	? (4,5)	103/No death causes presented
USA (12) 2000	Total: 5201 Males: 2239 Females: 2962	Community sample of elderly	65-100 (72.8)	10-item Center for Epidemiologic Studies Depression Scale (CES-D), cut point 8	1989 (6)	984/No death causes presented

Country (ref) Year of publication	Nr. of subjects in cohort	Setting	Age range (mean)	Measurement of depression Interview/diagnostic criteria	Baseline measurement (years of follow-up; mean)	Total number of deaths/number of suicides and accidents
Japan (29) 1997	2166	Community sample of elderly	60-74 ?	Zung Self-rating depression scale (SDS), cut point 48	1990-1991 (4)	77/2 suicides in the depressed group and 0 suicides in the non-depressed group
USA (13) 1992	1577	Community sample of elderly	≥65 (74.3)	20 item Center for Epidemiologic Studies Depression Scale (CES-D), cut point 16	1984 (3)	108/No death causes presented
Finland (26)	DSM-III: 1306 Zung: 1085	Community sample of elderly	65-85 ?	Zung self-rating depression scale (SDS), cut point 40/DSM-III criteria	? (5)	Zung: 189 DSM-III: 303/ No death causes presented
USA (14) 1994	1499	Community sample	≥18 ?	Depression index	1970-1971 (15)	?
USA (15) 1998	Females: 7518	Community sample of elderly	≥67 (71.4)	Geriatric Depression Scale short form, cut point 6	1988-1990 (average of 6)	871/ RR depressed vs not depressed for accidents and traumas: 6.3 (1.7-23.8)

Depression was identified in several ways. In some studies a depression questionnaire was used and in other studies depression was diagnosed according to a list of diagnostic criteria.

In eleven studies (7, 9, 11, 18-19, 21-22, 25-28) a depression questionnaire was used, but the diagnosis of depression was based on the presence or absence of a list of diagnostic criteria. If this was the case, we only mentioned the diagnostic criteria in the summary below as well as in table 2. In nine studies the diagnosis of depression was made according to DSM-III criteria (7, 9-10, 16, 19, 21-23, 26), in five studies the Centre for Epidemiologic Studies-Depression (CES-D) scale was used (6, 8, 12-13, 20) and in two studies the AGECAT computer diagnostic program was used (18, 25).

TABLE 2
Relation between depression and subsequent risk of dying in cohort studies: subgroup analyses

Variable	Number of studies	Chi-square test for homogeneity (p-value)	Summary estimated relative risk and (95% CI)
Sex			
Males	6	0.00	2.13 (1.17-3.88)
Females	7	0.00	1.58 (1.21-2.07)
Continent			
America	9	0.00	1.42 (1.07-1.88)
Europe	8	0.07	1.57 (1.32-1.87)
Australia	2	0.62	1.42 (1.05-1.92)
Asia	1	/	/
Years of follow-up			
≤ 5	13	0.00	1.68 (1.29-2.20)
5-10	4	0.00	1.42 (1.06-1.91)
≥ 10	1	/	/
Measurement of depression			
DSM-III	9	0.00	1.38 (1.11-1.73)
CES-D	4	0.00	1.38 (0.90-2.11)
AGECAT computer Diagnostic program	2	0.00	1.46 (0.98-2.18)
Others	5	0.00	2.18 (1.54-3.07)

Other measures used were the Feighner criteria for major depression (11), the revised version of Beck's Depression Inventory (24), the Geriatric Depression Scale short Form (15), the Depression Index (14), the 40-item OBD subscale of the MMPI (17), the ICD-10 criteria for depressive episodes (27) and the Zung-Self-rating depression scale (29).

Fifteen of the twenty-four studies had a follow-up period of five years or less (6, 8-9, 11, 13, 16, 18-22, 24-26, 29), four studies had a follow-up time varying from five to ten years (7, 12, 15, 23) and three studies had a follow-up time of ten years or more (10, 14, 17). One study had a follow-up time between three and six years (27) and in another this was between five and six years (28).

The percentages of people deceased during follow-up varied from 3.6% (29) to 58.1% (21).

The results of all studies proved a significant degree of heterogeneity that could not be explained by a number of study characteristics (table 2).

Results of individual studies

Table 3 shows the available unadjusted and adjusted risk estimates of all studies.

Nineteen studies reported outcome measures for males and females combined (6-10, 12-14, 16-19, 21-26, 28). Fourteen of these studies (6, 8, 10, 12, 16-19, 21-25, 28) reported a positive association for depression and subsequent mortality, which was significant in nine studies (6, 12, 17-19, 21-22, 24-25). One study (7) found a positive association between mortality and both recent and past depression. One study (26) reported the relative risks for the four age groups used in the study and showed a positive association for all groups, which was significant for the three lowest age groups. Three studies (9, 13-14) reported a negative association for depression and mortality of which none was significant. Five studies (8, 18, 21-23) also reported outcome measures for males and females separately. One of them (21) reported a positive significant association for both sexes, one (22) reported a positive association for both sexes, which was significant only for females, one study (23) reported a positive non-significant association for both sexes, one study (18), that reported on males only, showed a positive significant association and one study (8) reported a negative association for males and a positive association for females (both not significant).

TABLE 3
Results of prospective studies on depression and mortality

Country (ref) Year of publication	Nr. of deaths		Nr. of survivors		Crude RR of dying in depressed vs not depressed (95% CI)	Adjusted RR (95% CI)	Confounders in analyses	Remarks
	Depressed	Not depressed	Depressed	Not depressed				
Finland (16) 1998	4	86	22	859	1.69 (0.66-4.19)	1.80 (0.71-4.61)	MMSE-score	/
Denmark (17) 1996	?	?	?	?	?	1.59 (1.26-2.00)	Age and sex	/
USA (6) 1999	110	114	527	1738	2.81 (2.19-3.59)	1.42 (1.01-2.05)	Gender, age, education, Insurance coverage, immigrant status, language of interview, self reported chronic conditions and self-rated health	/
USA (7) 1994	39	1155	78	2288	0.99 (0.76-1.28)	2.01 recent depression ns 1.54 past depression s	Age and sex	/
USA (8) 1998	Total 97 Males 30 Females 67	Total 464 Males 218 Females 246	Total 515 Males 118 Females 397	Total 2691 Males 803 Females 1888	Total 1.08 (0.88-1.32) Males 0.95 (0.67-1.33) Females 1.24 (0.97-1.61)	Total 1.14 (0.91-1.42) Males 0.95 (0.64-1.41) Females 1.26 (0.96-1.66)	Age, gender, race, education, cognitive impairment, alcohol dependency, smoking, serum albumin level, and percentage of ideal bodyweight	/
UK (18) 1988	Total 23 Males 11 Females 12	Total 156 Males 72 Females 84	Total 95 Males 19 Females 76	Total 780 Males 309 Females 471	Total 1.17 (0.79-1.73) Males 1.94 (1.41-3.20) Females 0.90 (0.51-1.57)	Total 1.74 (1.03-2.94) Males 2.92 (1.14-7.49) Females ?	Age and sex	Adjusted RR= depressed vs well (organic disorders and neurosis are not included in the control group)
Norway (19) 1996	19	65	34	216	1.55 (1.01-2.34)	1.9 (1.0-3.6)	No confounders	/

Country (ref) Year of publication	Nr. of deaths	Nr. of survivors	Nr. of deaths	Nr. of survivors	Crude RR of dying in depressed vs not depressed (95% CI)	Adjusted RR (95% CI)	Confounders in analyses	Remarks
USA (9) 1989	1	43	91	1471	0.39 (0.06-2.63)	0.41 ns	No confounders	/
France (20) 1999	?	?	?	?	?	Total ? Males 1.49 (1.1-1.9) Females 1.25 (1.0-1.6)	Age, education, health, health behaviour, social support, satisfaction and social network index	/
USA (10) 1997	14	10	613	544	1.10 (0.76-1.53)	1.27 (0.54-2.97)	Baseline sociodemographic characteristics, medical conditions and functional status	Adjusted RR= depressed vs well (depression syndrome with sadness and non-dysphoric depression are not included in control group)
Australia (27) 1997	8	23	198	771	1.26 (0.68-2.29)	?	?	/
Australia (28) 1991	19	14	75	120	1.50 (1.05-2.09)	1.53 ns	No confounders	/
Germany (21) 1999	?	?	?	?	?	Total 1.51 (1.10-2.07) Males 1.77 (1.07-3.38) Females 1.44 (1.00-2.06)	No confounders	/
USA (11) 1988	Total 50 Males 18 Females 32	Total 96 Males 25 Females 71	Total 23 Males 5 Females 18	Total 141 Males 52 Females 89	Total 2.44 (1.57-3.79) Males 4.77 (1.92-11.78) Females 1.85 (1.11-3.08)	Males P< 0.01 Females P<0.05	?	/
Netherlands (22) 1999	Total 15 Males 4 Females 11	Total 46 Males 10 Females 36	Total 546 Males 343 Females 203	Total 2449 Males 1121 Females 1328	Total 1.35 (0.86-2.09) Males 1.22 (0.56-2.98) Females 1.77 (1.03-2.98)	Total 2.32 (1.38-3.89) Males 1.71 (0.63-4.58) Females 2.57 (1.39-4.74)	Age and sex	Adjusted RR= Depressed vs well (minor depression is not included in the control group)

Country (ref) Year of publication	Nr. of deaths	Nr. of survivors	Crude RR of dying in depressed vs not depressed (95% CI)	Adjusted RR (95% CI)	Confounders in analyses	Remarks
Finland (23) 1997	Total 81 Males 34 Females 47	Total 203 Males 96 Females 107	Total 209 Males 67 Females 142	Total 779 Males 321 Females 458	Total 1.35 (1.08-1.69) Males 1.46 (1.09-2.01) Females 1.31 (0.97-1.77)	Total 1.3 (0.98-1.65) Males 1.2 (0.94-2.06) Females 1.2 (0.85-1.69)	Age, sex, marital status, education and smoking	/
Italy (24) 1991	48	64	346	743	1.54 (1.08-2.19)	P< 0.05	No confounders	/
Spain (25) 1999	37	177	68	709	1.76 (1.31-2.35)	3.0 (1.7-5.3)	Sex, age, educational level and physical illness	Adjusted RR= depressed vs well (neuroses and dementia are not included in control group)
USA (12) 2000	248	734	788	3422	1.36 (1.19-1.54)	1.24 (1.06-1.46)	Sociodemographic factors, prevalent clinical disease, subclinical disease indicators and biological or behavioural risk factors	/
Japan (29) 1997	Total 29 Males 20 Females 9	Total 48 Males 29 Females 19	Total 229 Males 73 Females 156	Total 1860 Males 901 Females 959	Total 4.47(2.87-6.94) Males 6.90 (4.05-11.64) Females 2.81 (1.29-6.08)	Total ? Males 13.00 s Females 4.31 s	No confounders Severe depressed vs well (minor depression not included in control group)	/
USA (13) 1992	11	97	200	1269	0.73 (0.40-1.34)	0.82 (0.44-1.52)	Age, sex, measures of changes in health, changes in functional status and changes in number of chronic medical conditions and social support	/

Note: The "Nr. of deaths" header spans the first two data sub-columns and "Nr. of survivors" spans the next two data sub-columns.

Country (ref) Year of publication	Nr. of deaths		Nr. of survivors		Crude RR of dying in depressed vs not depressed (95% CI)	Adjusted RR (95% CI)	Confounders in analyses	Remarks
Finland (26) 1998	Total 97 65 20 75 21 80 24 85 32	Total 92 65 29 75 17 80 21 85 25	Total 246 65 144 75 48 80 30 85 24	Total 650 65 480 75 87 80 56 85 27	Total 2.28 (1.77-2.94) 65 2.14 (1.24-3.67) 75 1.86 (1.06-3.26) 80 1.63 (1.01-2.61) 85 1.19 (0.83-1.71)	Total ? 65 2.49 (1.40-4.44) 75 2.24 (1.08-4.64) 80 2.13 (1.02-2.45) 85 1.44 (0.67-3.08)	?	/
USA (14) 1994	?		?		?	0.91 (0.71-1.17)	Age, sex, socio-economic status, length of health plan membership, subjective health status and smoking	/
USA (15) 1998	111	760	362	6285	2.18 (1.82-2.59)	1.47 (1.14-1.88)	Age Further adjustment for marital status, living status, education, alcohol use, physical activity, social support, use of estrogen, benzodiazepine, barbiturates and body mass index does not affect the association	/

s: significant
ns: not significant
rr: relative risk

Four studies (11, 15, 20, 29) only reported separate outcome measures for males and females. Three of them (11, 20, 29) reported a positive significant association for both sexes, and one study (15), that reported about females only, also showed a positive significant association.

The relative risk of dying slightly decreases with increasing period of follow-up, losing statistical significance if the follow-up was longer than 10 years. There is no difference between the continents. Between studies using different methods to identify presence or absence of depression, no increased summary relative risk was found for CES-D and the AGECAT Computer Diagnostic Program. An increased summary relative risk of 1.38 (95% CI 1.11-1.73) was found for DSM-III. For the group 'others' (including the Feighner criteria for major depression, the revised version of Beck's Depression Inventory, the Geriatric Depression Scale Short Form, the Depression Index, the 40-item OBD subscale of the MMPI, the ICD-10 criteria for depressive episode and the Zung-Self-rating depression scale) a summary relative risk of 2.18 (95% CI 1.54-3.07) was found.

Statistical pooling

Twenty studies (6-13, 15-16, 18-19, 22-29) were included in the statistical pooling, of which one presented data for females only (15).

The overall summary relative risk of dying in people with and without depression was 1.56 (1.31-1.85). Table 2 presents the results of the chi-square test for homogeneity and the summary relative risks for the different subgroups.

Discussion

In this review, results from twenty-four prospective studies on depression and mortality have been summarized. Nine out of twenty-four studies reported a significant positive adjusted relative risk indicating an increase of the mortality risk following depression. No study showed a significant negative association. The majority of studies showed a positive non-significant association between depression and mortality. Statistical pooling based on twenty studies with complete data revealed a significant positive association between depression and subsequent mortality, with a summary relative risk (95% CI) of 1.56 (1.31-1.85). The studies that reported data on males and females separately showed summary estimated relative risks (95% CIs) of 2.13 (1.17-3.88) and 1.58 (1.21-2.07) respectively. The effect size diminished with increasing

follow-up time. It was above 1.0, however, in all subgroups. Statistical significance was lost in the study with more than 10 years of follow-up.

Four studies could not be included in the statistical pooling because of missing data. Three of these studies reported a significant positive adjusted risk estimate varying from 1.25 to 1.59 and one study reported a non-significant negative association of 0.91. Including these studies could have resulted in a slightly lower summary estimated relative risk.

According to our funnel plot, studies with a relative risk around or below 1.0 may have been missed due to publication bias (figure 1). The plot suggests that this could be the case more specifically in studies with a sample size below 1000. However, removing all studies with a sample size below 1000 (with a relative risk around or above 1.50) (16, 19, 25, 28) and retaining all other studies resulted in a similar summary relative risk of 1.54 (1.26-1.89).

There is always the possibility that studies showing no or only weak associations have not been published and since we did not identify unpublished studies, they are not included in this review.

There are important differences among the studies in number of subjects, setting of cohort, identification of the absence or presence of depression, length of follow-up and the confounders included in the multivariate analysis, which might partly explain the differences in outcome. We performed subgroup analyses based on sex, continent, years of follow-up and measurement of depression. The results in the different subgroups did not differ very much from the overall summary relative risk. However, the summary estimated relative risks for men and for the depression measurement 'others' were somewhat higher than the overall measure and the positive associations found for the depression measurements CES-D and AGECAT were not significant.

How can the increased mortality risk reported in most studies be explained? Only eight out of twenty-four studies presented data on suicidal and accidental deaths, of which only four showed separate figures for depressed and non-depressed people. In three of these four studies, suicidal and accidental deaths accounted for less than 3% and in one study they accounted for 6.9% of the mortality in the depressed group. In the non-depressed group, three out of four studies showed no mortality due to suicides and accidents and in one study suicidal and accidental deaths accounted for 0.6% of the mortality. In one of the eight studies a relative risk (and corresponding 95% CI) of dying from accidents and traumas of 6.3 (1.7-23.8) for depressed vs not depressed was reported.

Since only a few studies reported on suicidal and accidental deaths, it is difficult to draw firm conclusions. It seems unlikely, however, that the increased mortality risk in the depressed group can be completely explained by an increase in suicidal and accidental deaths.

The presence of comorbidity could not be taken into account in this review. However, depression has been found to adversely affect endocrine, neurological and immune processes, which enhance susceptibility to disease and eventually may lead to death (6, 22). Depression may also adversely affect the outcome of a physical disease (30) and especially coronary heart disease and heart failure (31). In some cases depression may be an early sign of a medical condition as has been described for Parkinson's disease (32).

Intermediate factors between depression and increased mortality risk probably are unhealthy behavioural patterns. Depressed people were found to be less physically active, were more often smokers, alcohol and drug abusers and tended to have more extreme BMI values (6). They were also found to be less likely to comply with treatment recommendations (6, 33) and more likely to withdraw themselves from others and therefore lack social contacts and support, which may lead to an increased susceptibility to multi-morbidity and mortality (34).

In summary, however, this review supports the hypothesis that depression in the community might lead to a 50% increased total mortality risk.

Acknowledgements

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