Depression status, medical comorbidity and resource costs

Evidence from an international study of major depression in primary care (LIDO)[†‡]

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Background Despite the burden of depression, there remain few data on its economic consequences in an international context.

Aims To explore the relationship between depression status (with and without medical comorbidity), work loss and health care costs, using cross-sectional data from a multi-national study of depression in primary care.

Method Primary care attendees were screened for depression. Those meeting eligibility criteria were categorised according to DSM–IV criteria for major depressive disorder and comorbid status. Unit costs were attached to self-reported days absent from work and uptake of health care services.

Results Medical comorbidity was associated with a 17–46% increase in health care costs in five of the six sites, but a clear positive association between costs and clinical depression status was identified in only one site.

Conclusions The economic consequences of depression are influenced to a greater (and considerable) extent by the presence of medical comorbidity than by symptom severity alone.

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[†]See editorial, pp. 92–94, this issue.

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Despite ample evidence for the efficacy of antidepressant medications and structured forms of psychotherapy, a series of international studies have documented the modest rates of recognition and effective treatment attained in primary care for people suffering from depression (Thornicroft & Sartorius, 1993; Lepine *et al*, 1997; Simon *et al*, 1999). A manifest implication of these findings is that depression contributes heavily to estimates of national and global burden of disease (Vos & Mathers, 2000). However, assessment of the economic consequences of depression via cost-of-illness studies at the population level (Kind & Sorensen, 1993; Rice & Miller, 1995) or clinical trials at the individual level (Lave *et al*, 1998; Simon *et al*, 1995; Simpson *et al*, 2000) have been restricted largely to industrialised countries to date. Thus, there remains a paucity of information on the economic consequences of depression in an international context, including patterns of resource consumption, its effect on labour participation and the impact of comorbidity on work loss or health care needs.

METHOD

The overall aim of the Longitudinal Investigation of Depression Outcomes (LIDO) study was to assess associations between quality of life and economic and depression outcomes, based on a multi-national observational study with a prospective cohort of primary care patients with depression (Herrman *et al*, 2002). The specific objectives of the economic dimension of the LIDO study were: to develop a research method for collection of individual service utilisation and costs data, and site-level socio-demographic and service profiles; to describe and compare service utilisation and cost differences within and between sites; and to explore site-specific and cross-cultural relationships between service costs, depression symptoms, quality of life and functioning. Further description of the methods used and examination of the longitudinal relationship between costs, depression and treatment are reported elsewhere (Chisholm *et al*, 2001*a*). The focus of the present paper is a cross-sectional baseline analysis of costs, depression status and comorbidity. This takes advantage of the larger sample of subjects who met the initial eligibility criteria (depressive symptoms at baseline assessment) but who did not form part of the longitudinal investigation of cases meeting the full DSM–IV (American Psychiatric Association, 1994) criteria for major depressive disorder (see Simon *et al*, 2002).

Sampling strategy

Patients attending primary care clinics in six participating sites (Be'er Sheva, Israel; Barcelona, Spain; Porto Alegre, Brazil; Melbourne, Australia; St Petersburg, Russia; Seattle, WA, USA) were approached systematically in person by the primary care physician, clinic or research staff and invited to complete a screening assessment package, which was scored for initial eligibility (a score of 16 or greater on the Center for Epidemiologic Studies – Depression rating scale, CES–D; Radloff, 1977). In order to undertake subgroup analyses of gender differences, booster sampling of men was carried out in each site (a target quota of one-third of recruited subjects). Written informed consent was obtained from participating subjects following a description of the study. For patients meeting the initial eligibility criteria, a baseline assessment was conducted that included administration of a depression diagnostic instrument (Composite International Diagnostic Interview, version 2.1, CIDI; Weiller *et al*, 1994) and other measures of socio-demographic status and service contact. Patients with a chronic medical or psychiatric comorbid condition were eligible, but those with a known organic or major psychiatric disorder (dementia, psychosis, bipolar disorder) were excluded. A concurrent conditions checklist was used to identify subjects with one or more out of 12 major chronic medical conditions (Wells *et al*, 1991), comorbid anxiety was assessed via the Hopkins Symptom Checklist (SCL–90, with a cut-off score of 1.7; Derogatis *et al*, 1976) and high alcohol use was defined as at least 21 units/week for men, 14 units/week for women or at least six drinks on a single occasion in the previous month.

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Functional status was assessed using the 12-item Short Form Health Survey (SF–12) physical component score (Ware *et al*, 1995). Patients receiving treatment for depression currently or in the previous 3 months were excluded from the study, so that the reference population for the analysis is that of currently untreated cases of depression seen in primary care.

Principles and processes of service costing

Measurement of resource use was carried out via the administration of a service receipt schedule adapted specifically for use in this project from the Client Service Receipt Inventory (CSRI; Chisholm *et al*, 2001*b*). A range of primary care, psychiatric, social and general medical services was identified that gave a comprehensive profile of potential service receipt for the patient population in the six sites (Chisholm *et al*, 2001*a*). The three main categories of service contact were: primary care and out-patient services, which covered the frequency and average duration of contacts with primary care or mental health care professionals; day care services, provided to several patients at a time and usually offering a combination of treatment for problems related to mental illness; and in-patient hospital services, incorporating both psychiatric and general medical admissions.

A set of unit-cost templates was developed for computing the cost of services provided by both individual professionals and facilities. Site-specific unit costs for each service are listed in Table 1. Site-specific service costs were then converted into a common currency via purchasing-power parities (World Bank, 2000), which enables direct comparison of costs using the same metric (international dollars). In this paper, we primarily report cost results in national currency units because the focus is more on site-specific rather than pooled relationships.

Lost opportunities for employment were assessed via self-reported days absent from work. The costs of lost employment were estimated by multiplying days absent from work by the local wage rate for the occupational category of the patient. Other indirect costs, such as reduced productivity while at work or informal care support, were not collected in this study because of expected measurement difficulties at the international level.

Analysis

The sampled population in each site was split into four groups: (A) subclinical depression (CES–D score >16) but no medical comorbidity; (B) subclinical depression (CES–D score >16) with medical comorbidity; (C) clinical depression (CIDI positive) but no medical comorbidity; (D) clinical depression (CIDI positive) with medical comorbidity. This enabled us to test four hypotheses: that individuals with clinical depression consume more resources and have greater absence from work than those with subclinical depression, either discrete/non-comorbid ($C>A$) or comorbid ($D>B$); and that medical comorbidity has a cost-raising influence on health care use or work loss, for both subclinical depression ($B>A$) and clinical depression ($D>C$).

Total health care costs were made up of three categories: mental health out-patient costs (contact with a psychiatrist, psychologist or other mental health worker, and attendance at a day care programme); general medical out-patient visits (primary care doctor, non-mental health specialist physician or other health care worker such as a nurse practitioner, plus day hospital attendance for physical health problems); and general medical in-patient care (psychiatric admission in the 3 months prior to baseline would have excluded the subject from the study). Costs of out-patient services were adjusted for the average duration of visits.

Analyses of variance (with the Scheffé test for pairwise comparisons) and chi-squared test statistics were used for testing bivariate mean and proportional differences between the four analytical groups A–D, respectively. Owing to the skewed

Table 1 Site-specific unit costs of services

Service category	Measurement unit	Site-specific unit costs (local currencies)					
		Barcelona (peseta) PPP=129.5	Be'er Sheva (shekel) PPP=3.6	Melbourne (Australian $) PPP=1.4	Porto Alegre (real) PPP=0.8	Seattle (US $) PPP=1.0	St Petersburg (rouble) PPP=2.8
Primary care provider (GP, family doctor)	10 min of direct contact	830	53	25	15	28	2
Other primary health care worker (nurse)	10 min of direct contact	680	13	9	9	10	1
Psychiatrist	10 min of direct contact	860	29	33	15	22	2
Psychologist/therapist	10 min of direct contact	840	16	82	8	13	NA
Other mental health worker (e.g. MH nurse)	10 min of direct contact	670	13	8	9	11	NA
Other specialist physician/consultant	10 min of direct contact	830	160/visit	32.50	15	30	2
Day hospital (physical health)	Day's attendance	22 132	771	119	70	125/h	46.5
Day hospital (mental health)	Day's attendance	17 605	165	NA	70	248	31.5
Day care (community mental health)	Day's attendance	5636	140	81	70	152	NA
Psychiatric hospital ward	In-patient day	12 636	363	NA	NA	432	57
Psychiatric ward of general hospital	In-patient day	21 879	1033	297	95	584	42
Medical ward of general hospital	In-patient day	28 559	1389	583	208	824	21
Emergency ward (non-psychiatric)	Attendance	14 257	436	100	29	150	31

GP, general practitioner; MH, mental health; NA, not available or not used by sample population; PPP, purchasing-power parity: values are the conversion rates required to transform costs into US $ (source: World Bank, 2000: Table 5.6).

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distribution of cost data, confidence intervals for means were derived using bootstrapping, a non-parametric approach that avoids strong distributional assumptions by employing large numbers of re-sampling computations (Efron & Tibshirani, 1993). In order to adjust for key socio-demographic and clinical characteristics, total costs of health care were subsequently entered into a linear regression analysis in each site (using age, gender, marital status, education and employment as covariates alongside CIDI depression status, and dummy variables for comorbid anxiety and high alcohol use as well as chronic medical illness). A variety of different model specifications were fitted, including ordinary least squares (OLS), with both an untransformed and log-transformed dependent variable, and also generalised linear modelling with a gamma error distribution and a log-link function. Our chosen model specification was an OLS regression with the log of total service cost (+1, to avoid zero values for cost), which satisfied distributional assumptions (as well as homoscedasticity and independence), provided slightly improved explanatory power and allowed simplified inter-site comparison in terms of proportionate effects of specified variables on service costs (Diehr *et al*, 1999; Knapp *et al*, 2002).

RESULTS

Clinical characteristics of the sampled population

Across the six participating sites, a total of 18 489 screens were carried out among primary care attendees, of whom 4662 (25%) met the study eligibility criteria (CES–D > 16, and not treated in the previous 3 months). Out of the 13 827 non-eligible screened subjects, 63% had a CES–D score < 16, 10% were already being treated for depression and 2% expected to be moving away within the next year. Half of the eligible population agreed to participate in the study, giving a baseline study sample of 2359 primary care patients with untreated depression. Administration of the CIDI diagnostic interview revealed that 1193 subjects met the full DSM–IV diagnostic criteria for major depressive disorder (hereafter referred to as 'clinical depression'), whereas 166 subjects did not meet these criteria but nevertheless had depressive symptoms ('subclinical depression'). The mean CES–D scores for the two groups were 29.9 (s.d.=10.8) and 17.1 (s.d.=8.7), respectively, which is a clinically and statistically significant difference (t=31.6; P<0.001). Further splitting of the depression sample according to medical comorbidity status revealed that the largest proportion of cases belonged to the category of comorbid clinical depression (group D; an inter-site range of 21–43%), followed by comorbid subclinical depression (group B; 21–35%), non-comorbid subclinical depression (group A; 12–28%) and non-comorbid clinical depression (group C; 11–25%).

Socio-demographic characteristics of the sampled population

Comparison of the socio-demographic characteristics of the sampled populations who met the eligibility criteria for the study in each site is given in Table 2. The mean age of subjects was close to 40 years in each site except for St Petersburg, where the mean was 47 years (s.d.=16.2). Subjects with comorbid depression were appreciably older than those with non-comorbid depression, as were those with subclinical as opposed to clinical depression. The average number of years of schooling for the total sample in each site ranged from 9.3 (s.d.=3.4) in Porto Alegre to 13.7 (s.d.=2.9) in St Petersburg; in all six sites, subjects with comorbid clinical depression had fewer years of schooling. The striking similarity with respect to the gender of the sampled populations – in each of the six sites, women constituted two-thirds to three-quarters of the sample – is an artefact of the booster sampling of male attenders. The proportion of subjects who were married ranged from one-quarter in Melbourne to two-thirds in Be'er Sheva, but in all but the latter site, the subjects with clinical depression were more likely to be unmarried. The proportion of study subjects in employment ranged from approximately 50% in Porto Alegre and St Petersburg to 67% in Seattle, with rates consistently lower among the comorbid groups.

Rates and costs of resource utilisation

Table 3 provides a breakdown of the (unadjusted) rates of contact and costs of resource use across the six sites. Rates of contact between sites were 5–14% for mental health out-patient visits, 94–100% for general medical/primary care visits and 5–18% for in-patient admissions. Across the six sites, mean utilisation for the six sampled populations in the 3 months preceding baseline was 0.2–0.7 for mental health out-patient visits, 1.5–8.0 for medical out-patient or primary care attendances and 0.1–0.2 for in-patient days (not tabulated). Both the rate (%) and amount of contact were typically highest among subjects with clinical depression who had a medical and/or psychiatric comorbidity. The mean costs of this resource utilisation (for the sampled populations as a whole, not just service users) are reported in Table 3 (costs are expressed in national currencies, but can be converted into US dollars or other monetary units using the set of purchasing-power-parity conversion factors provided in Table 1). Focusing on total health care costs – similar findings are obtained for the three subcategories of resource cost – we find the following.

(a) *Hypothesis 1 (C > A): Clinical depression is more costly than subclinical depression (no medical comorbidity).* In all sites except St Petersburg costs are higher, most notably in Be'er Sheva and Porto Alegre (40% higher) and Barcelona (300%). However, none of these differences is statistically significant at the 5% level.

(b) *Hypothesis 2 (D > B): Clinical depression is more costly than subclinical depression in comorbid cases.* Costs are higher in five of the six sites (10–50%); in Be'er Sheva, costs are 40% lower. Again, these differences do not reach statistical significance.

(c) *Hypothesis 3 (B > A): Comorbidity increases the costs of subclinical depression.* In all sites except St Petersburg costs are appreciably higher: by a factor of 2 in Melbourne, Porto Alegre and Seattle, a factor of 3 in Be'er Sheva and a factor of 4 in Barcelona. Using the Scheffé test for pairwise comparisons, the difference or total health care costs reached statistical significance only in Seattle (and also in Melbourne for general medical out-patient costs).

(d) *Hypothesis 4 (D > C): Comorbidity increases costs in clinical depression.* Costs are considerably higher in all sites (over 100% higher in Melbourne and Seattle; 20–50% higher elsewhere). Again, the difference reached statistical significance only in Seattle.

An overview of the cost differences for each hypothesis and site is given in Fig. 1.

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Table 2 Socio-demographic characteristics of sampled populations

Variable	Be'er Sheva		Barcelona		Melbourne		Porto Alegre		Seattle		St Petersburg	
	n	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)	*n*	Mean (s.d.)
Age												
A. Subclinical depression, discrete	104	37.9 (12.4)	134	35.7 (12.8)	85	35.0 (10.9)	101	36.4 (13.0)	66	36.1 (11.9)	36	38.4 (16.3)
B. Subclinical depression, comorbid	95	46.9 (15.7)	124	51.0 (14.5)	107	46.1 (16.3)	82	46.1 (12.4)	125	48.2 (15.8)	107	50.9 (14.0)
C. Clinical depression, discrete	75	34.5 (11.0)	116	32.8 (10.4)	87	32.1 (10.3)	90	34.4 (11.5)	68	33.5 (10.8)	33	37.4 (14.1)
D. Clinical depression, comorbid	109	44.6 (14.0)	98	47.8 (14.2)	158	41.2 (13.9)	118	42.9 (14.1)	107	43.1 (14.5)	134	48.6 (16.6)
Total	383	41.4 (14.3)	472	41.5 (15.2)	437	39.4 (14.3)	391	39.9 (13.6)	366	41.8 (15.0)	310	47.0 (16.2)
F		16.116*		55.960*		21.391*		16.490*		20.855*		10.735*
Years of education												
A. Subclinical depression, discrete	104	12.6 (2.3)	134	11.1 (3.3)	85	13.7 (3.1)	101	9.7 (3.2)	66	13.4 (2.1)	36	14.4 (2.1)
B. Subclinical depression, comorbid	95	12.0 (3.0)	124	9.9 (3.9)	107	11.6 (4.0)	82	9.2 (3.6)	125	13.5 (2.6)	107	14.1 (2.8)
C. Clinical depression, discrete	75	11.8 (2.4)	116	10.7 (3.1)	87	13.4 (3.8)	90	9.5 (3.4)	68	13.4 (1.9)	33	14.0 (2.0)
D. Clinical depression, comorbid	109	11.3 (2.8)	98	9.6 (3.8)	158	11.8 (12.4)	118	8.9 (3.2)	107	13.0 (2.2)	134	13.0 (3.2)
Total	383	11.9 (2.7)	472	10.4 (3.6)	437	12.4 (3.8)	391	9.3 (3.4)	366	13.3 (2.3)	310	13.7 (2.9)
F		4.679*		4.860*		8.833*		1.207		1.077		4.091*
Female gender												
A. Subclinical depression, discrete	104	60.6%	134	71.6%	85	69.4%	101	78.2%	66	63.6%	36	58.3%
B. Subclinical depression, comorbid	95	55.8%	124	66.9%	107	61.7%	82	72.0%	125	64.0%	107	70.1%
C. Clinical depression, discrete	75	69.3%	118	77.6%	87	63.2%	90	78.9%	68	66.2%	33	66.7%
D. Clinical depression, comorbid	109	63.3%	98	67.3%	158	65.8%	118	72.0%	107	72.9%	134	79.1%
Total	383	61.9%	472	71.0%	437	65.0%	391	75.2%	366	66.9%	310	72.3%
χ^2		3.429		4.098		1.413		2.248		2.547		7.380†
Married												
A. Sub-clinical depression, discrete	104	71.2%	134	48.5%	85	31.8%	101	42.6%	66	56.1%	36	50.0%
B. Subclinical depression, comorbid	95	60.0%	124	70.2%	107	29.9%	82	68.3%	125	50.4%	107	47.7%
C. Clinical depression, discrete	75	62.7%	116	45.7%	87	19.5%	90	48.9%	68	47.1%	33	39.4%
D. Clinical depression, comorbid	109	71.6%	98	61.2%	158	24.7%	118	53.4%	107	42.1%	134	43.3%
Total	383	68.8%	472	56.1%	437	26.3%	391	52.7%	366	48.4%	310	45.2%
χ^2		4.563		19.245*		4.290		12.699*		3.524		1.245
Employed												
A. Subclinical depression, discrete	104	70.2%	134	71.6%	85	69.4%	101	54.5%	66	78.8%	36	69.4%
B. Subclinical depression, comorbid	95	52.6%	124	41.1%	107	57.0%	82	40.2%	125	59.2%	107	47.7%
C. Clinical depression, discrete	75	61.3%	116	81.0%	87	67.8%	90	52.2%	68	76.5%	33	69.7%
D. Clinical depression, comorbid	109	43.1%	98	46.9%	158	56.3%	118	48.3%	107	64.5%	134	47.8%
Total	383	56.4%	472	60.8%	437	61.3%	391	49.1%	366	67.5%	310	52.6%
χ^2		17.154*		54.571*		6.392†		4.113		10.694*		10.270*

*$P<0.05$. †$P<0.10$.

Table 3 Rates and costs of resource utilisation (national currencies)

	Be'er Sheva (shekel)			Barcelona (peseta)			Melbourne (Australian $)			Porto Alegre (real)			Seattle (US $)			St Petersburg (rouble)		
	n	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)
Mental health out-patient care visits																		
A. Subclinical depression, discrete	104	3.8%	25.7 (0.9–74.2)	134	6.7%	594.7 (190.6–1276)	85	17.6%	54.4 (24.2–101.1)	101	8.9%	25.3 (5.8–55.1)	66	4.5%	19.5 (0.0–59.9)	36	5.6%	3.7 (0.0–12.4)
B. Subclinical depression, comorbid	95	4.2%	90.8 (0.2–309.7)	124	3.2%	8716 (41.0–31 860)	107	7.5%	36.5 (4.7–103.9)	82	3.7%	8.5 (0.0–23.1)	125	4.8%	82.1 (3.0–228.1)	107	3.7%	0.2 (0.0–0.5)
C. Clinical depression, discrete	75	8.0%	14.7 (2.2–39.6)	116	5.2%	206.1 (47.9–468.8)	87	14.9%	39.4 (10.9–95.9)	90	12.2%	43.3 (10.7–99.2)	68	14.7%	56.5 (12.4–152.1)	33	6.1%	23.3 (0.0–88.7)
D. Clinical depression, comorbid	109	8.3%	19.7 (5.6–43.1)	98	5.1%	468.1 (47.4–1455)	158	16.5%	91.6 (43.6–161.9)	118	11.0%	72.2 (29.0–142.3)	107	11.2%	50.0 (21.9–86.6)	134	6.0%	1.9 (0.3–5.4)
Total	383	6.0%	38.0 (9.5–110.0)	472	5.1%	2607 (236.1–9261)	437	14.2%	60.5 (36.2–90.7)	391	9.2%	40.1 (22.8–65.4)	366	8.5%	56.7 (26.2–108.8)	310	5.2%	3.8 (0.7–10.3)
F^1			0.591			0.884			1.047			1.756			0.402			2.639* (D<C)†
General medical out-patient/primary care visits																		
A. Subclinical depression, discrete	104	91.3%	363.4 (278.2–480.6)	134	98.5%	4107 (3288–5325)	85	100%	201.1 (147.5–292.5)	101	96.0%	136.8 (102.3–184.6)	66	100%	319.6 (250.5–395.5)	36	94.4%	22.4 (15.0–33.5)
B. Subclinical depression, comorbid	95	97.9%	934.2 (543.5–1747.8)	124	96.8%	10 006 (5071–20 449)	107	100%	349.8 (281.9–434.2)	82	95.1%	151.0 (105.4–227.3)	125	99.2%	569.5 (447.8–720.8)	107	92.5%	26.6 (21.6–32.8)
C. Clinical depression, discrete	75	90.7%	727.7 (485.0–1079)	116	99.1%	14 788 (27 151–47 769)	87	98.9%	209.6 (163.0–276.4)	90	95.6%	150.7 (118.2–191.4)	68	100%	356.5 (276.1–458.4)	33	90.9%	33.7 (14.6–63.2)
D. Clinical depression, comorbid	109	96.3%	939.3 (725.9–1191)	98	99.0%	14 385 (7479–29 753)	158	100%	297.5 (254.9–351.2)	118	94.9%	229.9 (181.5–289.6)	107	99.1%	600.7 (470.3–760.3)	134	97.8%	44.5 (27.3–70.2)
Total	383	94.3%	740.2 (595.7–956.8)	472	98.3%	10 416 (5792–18 649)	437	99.8%	274.0 (245.3–305.1)	391	95.4%	171.1 (149.6–198.9)	366	99.5%	494.0 (428.4–567.0)	310	94.8%	34.6 (26.9–47.2)
F^1			2.455†			0.620			4.777* (B>A)*			3.249*			4.176*(B>A)†			1.146
General medical in-patient care days																		
A. Subclinical depression, discrete	104	8.7%	676.2 (212.4–1336)	134	3.7%	1597 (212.8–4416.9)	85	10.6%	72.3 (14.1–175.8)	101	2.0%	8.2 (0.0–27.1)	66	1.5%	27.2 (0.0–105.8)	36	22.2%	94.5 (33.8–173.9)
B. Subclinical depression, comorbid	95	14.7%	2079.0 (710.4–4632)	124	5.6%	6909 (1744–16 855)	107	9.3%	282.4 (120.1–499.2)	82	7.3%	165.2 (35.1–369.0)	125	8.0%	170.7 (61.6–347.0)	107	17.8%	44.3 (23.0–71.1)
C. Clinical depression, discrete	75	10.7%	721.2 (254.9–1345)	116	5.2%	6278 (799–17 219)	87	6.9%	83.9 (16.9–180.0)	90	4.4%	50.8 (35.1–369.0)	68	0%	0.0 (0.0–0.0)	33	12.1%	22.6 (0.0–60.2)
D. Clinical depression, comorbid	109	9.2%	928.8 (315.3–1833)	98	15.3%	17 192 (7878–31 286)	158	15.8%	328.8 (130.4–667.5)	118	6.8%	41.5 (11.6–82.6)	107	11.2%	242.1 (96.2–452.9)	134	18.7%	55.3 (33.2–86.8)
Total	383	10.7%	1104.8 (646.9–1796)	472	7.0%	7381 (4229–11 718)	437	11.4%	218.8 (133.1–340.2)	391	5.1%	61.0 (27.2–107.8)	366	6.3%	134.0 (72.6–219.1)	310	18.1%	52.6 (37.6–70.2)
F^1			1.369			2.755*			1.519			2.537†(B>A)†			2.504†			1.526

(Continued)

Table 3 *(Continued)*

	Be'er Sheva (shekel)			Barcelona (peseta)			Melbourne (Australian $)			Porto Alegre (real)			Seattle (US $)			St Petersburg (rouble)		
	n	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)	*n*	Rate of contact	Mean cost (95% CI)
Total health care																		
A. Subclinical depression, discrete	104	92.3%	1065 (605–1767)	134	98.5%	6299 (4465–9576)	85	100%	327.8 (237.8–453.7)	101	97.0%	170.3 (125.6–228.3)	66	100%	366.4 (277.5–486.6)	36	94.4%	120.6 (56.4–203.1)
B. Subclinical depression, comorbid	95	97.9%	3104 (1520–5991)	124	96.8%	25 631 (11 238–48 905)	107	100%	668.7 (474.8–919.7)	82	95.1%	324.7 (165.2–551.5)	125	99.2%	822.3 (601.1–1078)	107	92.5%	71.1 (50.0–101.3)
C. Clinical depression, discrete	75	90.7%	1464 (842–2275)	116	99.1%	21 272 (5104–57 331)	87	98.9%	332.9 (240.5–451.6)	90	95.6%	245.9 (169.1–371.6)	68	100%	421.6 (320.0–546.0)	33	90.9%	79.5 (36.1–142.8)
D. Clinical depression, comorbid	109	96.3%	1888 (1218–2865)	98	99.0%	32 046 (18 489–49 983)	158	100%	736.7 (511.6–1089)	118	95.8%	343.6 (271.3–429.8)	107	99.1%	892.8 (678.9–1193)	134	97.8%	106.1 (72.0–152.5)
Total	383	94.5%	1883 (1373–2584)	472	98.3%	20 403 (13 166–30 704)	437	99.8%	560.1 (454.3–704.2)	391	95.9%	272.4 (225.7–337.5)	366	99.5%	686.2 (580.0–811.6)	310	94.8%	92.9 (73.0–117.3)
F^1	2.093†			1.593			3.066*			2.277†			4.990* (B>A, D>C)†			0.959		
Total for all cases (US $, PPP)	523			158			400			340			686			33		
Average per capita expenditure[2]	149%			52%			100%			318%			74%			53%		

Note: Costs are in national currencies: to convert costs into comparable (international) US dollars, divide by 1.4 (Australian $), 0.8 (Brazilian real), 3.6 (Israeli shekel), 2.8 (Russian rouble) and 129.5 (Spanish peseta).
1. Scheffé test used for *post hoc* pairwise comparison of hypothesised differences: *$P<0.05$; †$P<0.10$.
2. 1997 average national per capita expenditure figures (source: World Bank, 2000).

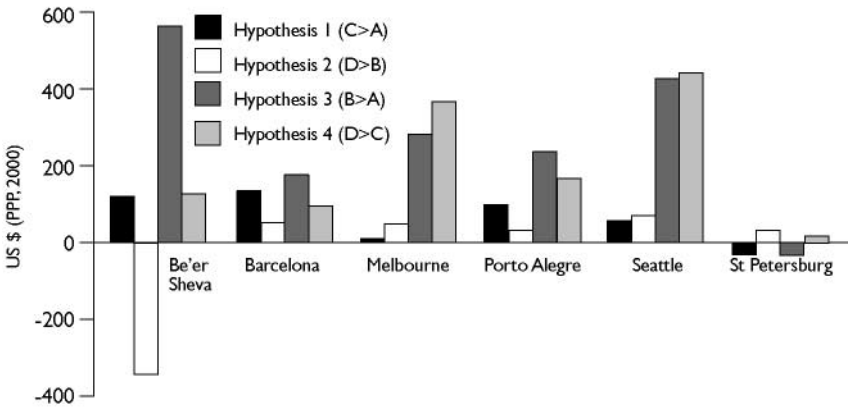

Fig. 1 Differences in health care costs for the 3 months prior to baseline assessment (US $, purchasing power parity (PPP), 2000): (A) subclinical depression, discrete; (B) subclinical depression, comorbid; (C) clinical depression, discrete; (D) clinical depression, comorbid.

Rates and costs of work disability

Incidence of self-reported days absent from work ranged from 20% of cases in Porto Alegre to 55% in Seattle, whereas the average number of days taken off work in the previous 3 months ranged from 1.4 days (s.d.=5.6) in Porto Alegre to 7.6 days (s.d.=15.3) in St Petersburg (Table 4). By attaching site- and occupation-specific daily wage rates to work absences, an estimate (in human capital) of the costs of lost productivity can be obtained. This approach reveals that the monetary value accorded to these lost work days constitutes an appreciable element of the overall economic costs of depression. In five of the six study sites the cost of lost work days was somewhat less than the total cost of health care, but nevertheless represented 15–40% of the total combined costs of health care and work loss. In the sixth site (Barcelona), lost work day costs were 75% greater than total health care costs.

With respect to the four subgroups, we found weak support for the hypothesised excess costs associated with clinical depression status: costs in the non-comorbid groups (Hypothesis 1: C>A) were similar in three of the sites but at least doubled in Be'er Sheva and Melbourne (difference not significant at the 5% level) and St Petersburg, whereas the costs in the comorbid groups (Hypothesis 2: D>B) were higher by a factor of 3 in Barcelona (Scheffé test: $P<0.05$), Melbourne and St Petersburg but actually lower in Be'er Sheva and Seattle. The hypothesised increase in the number and cost of lost work days among those with comorbid depression was not supported by these data (Hypotheses 3 and 4: B>A; D>C). In Be'er Sheva and Melbourne, costs were in fact significantly lower in the comorbid groups (Scheffé test: $P<0.05$).

Multivariate analysis

Six site-specific regression models were developed in order to assess the contribution of depression status and medical comorbidity towards excess costs of health care (Table 5). Using the natural logarithm of total health service cost as the dependent variable and controlling for key socio-demographic and clinical variables, we found a significant proportionate increase in cost attributable to being clinically depressed (as ascertained by the CIDI) in Porto Alegre (52%), a modest increase in Barcelona, Seattle and St Petersburg (4–18%) and a decrease in Be'er Sheva and Melbourne (4–16% less). With respect to medical comorbidity, there was a significant effect in Barcelona, Be'er Sheva, Melbourne and Seattle (costs increase by 24–46%) and a lesser effect in Porto Alegre (17% increase). In St Petersburg, costs were 15% lower in medically comorbid cases.

A range of other factors had an impact on costs but the only consistent finding was for the physical component score of the SF–12, which showed a statistically significant negative relationship in all sites, reflecting a lowering of costs as the score decreases towards no physical illness. Psychiatric comorbidity had a discernible effect in Seattle – anxiety increased costs by nearly 50%, whereas high alcohol use reduced costs by 35% – but elsewhere had no significant or consistent influence. Overall, the multivariate models had quite low explanatory power (adjusted R^2 values were 8–18%) and provided no consistent cost relationships across all sites other than the medical comorbidity and physical illness score.

DISCUSSION

Depression status, medical comorbidity and resource costs

In view of previous international studies indicating the high prevalence, enduring disability and undertreatment of depression in primary care (Thornicroft & Sartorius, 1993; Lepine *et al*, 1997; Simon *et al*, 1999), the LIDO study was undertaken to explore the cross-sectional and longitudinal relationship between depression symptoms, quality of life and economic outcomes in a number of diverse cultural settings. Using the baseline assessments of all subjects with depression who met the initial eligibility criteria, this paper addressed the question of whether depression severity or medical comorbidity are associated with higher health care costs and absence from work. By excluding those not currently treated for depression, we focused on the use of general medical services rather than the costs of depression treatment. Our primary finding is that, across the six international study sites, unadjusted levels and associated costs of resource utilisation and work disability show a clear (but often statistically non-significant) tendency to be higher in clinical *v.* subclinical depression and in medically comorbid *v.* discrete depression. Controlling for the effect of key socio-demographic and relevant clinical characteristics via site-specific regression analyses confirmed that medical comorbidity was associated with a 17–46% increase in health care costs in five of the six sites. However, such a clear positive association was not observed in relation to costs and clinical depression status. A potential explanation for the latter finding is that study subjects may not have met the full diagnostic criteria for major depressive disorder for the whole 3-month retrospective cost period, whereas by definition the presence of a chronic medical illness is less subject to fluctuation over time. In addition, the large amount of unexplained variance reduces our ability to detect differences associated with depression or medical comorbidity.

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Table 4 Rates and costs of days absent from work

	Be'er Sheva (shekel)			Barcelona (peseta)			Melbourne (Australian $)			Porto Alegre (real)			Seattle (US $)			St Petersburg (rouble)		
	%	Mean days (s.d.)	Mean cost (95% CI)	%	Mean days (s.d.)	Mean cost (95% CI)	%	Mean days (s.d.)	Mean cost (95% CI)	%	Mean days (s.d.)	Mean cost (95% CI)	%	Mean days (s.d.)	Mean cost (95% CI)	%	Mean days (s.d.)	Mean cost (95% CI)
A. Subclinical depression, discrete	33.7%	3.2 (8.1)	951 (516–1582)	32.1%	2.5 (6.7)	34 305 (20 390–55 136)	35.3%	2.7 (9.3)	372 (126–829)	23.8%	1.0 (2.7)	36 (16–65)	54.5%	4.2 (8.5)	487 (256–951)	33.3%	6.9 (15.4)	0.0 (0.0–0.0)
B. Subclinical depression, comorbid	34.7%	3.2 (9.5)	733 (295–1629)	13.7%	1.3 (4.8)	19 715 (8987–36 701)	21.5%	1.0 (2.5)	117 (60–201)	13.4%	1.5 (7.3)	47 (9–123)	49.6%	5.6 (13.5)	641 (386–1047)	28.0%	7.7 (16.1)	19 (0.0–51)
C. Clinical depression, discrete	45.3%	7.8 (14.5)	1897 (1171–2860)	30.2%	2.5 (7.8)	32 977 (19 049–54 304)	55.2%	5.8 (12.9)	861 (474–1396)	18.9%	1.0 (2.8)	35 (15–63)	64.7%	4.6 (8.2)	457 (283–699)	30.3%	6.6 (14.1)	39 (0.0–156)
D. Clinical depression, comorbid	26.6%	2.9 (8.1)	679 (365–1145)	27.6%	3.6 (9.7)	48 904 (23 852–85 479)	24.1%	2.8 (9.8)	316 (149–588)	21.2%	2.0 (7.4)	67 (29–129)	54.2%	5.0 (10.5)	420 (270–609)	37.3%	7.9 (15.1)	36 (14–70)
Total	34.2%	4.0 (10.1)	1005 (750–1351)	25.8%	2.4 (7.3)	33 177 (24 765–43 912)	31.8%	2.9 (9.4)	387 (259–534)	19.7%	1.4 (5.6)	47 (30–71)	54.6%	5.0 (10.9)	515 (389–658)	32.9%	7.6 (15.3)	26 (11–46)
F[1]		4.440* (D<C)*	2.983* (D>C)†		1.910 (D>B)*	1.381		4.334* (D<C)†	4.356* (D<C)†		0.841	0.603		0.272	0.601		0.100	0.728

Note: Sample *n* for each site are the same as in Tables 2 and 3. Costs are in national currencies: to convert costs into comparable (international) US dollars, divide by 1.4 (Australian $), 0.8 (Brazilian real), 3.6 (Israeli shekel), 2.8 (Russian rouble) and 129.5 (Spanish peseta).

1. Scheffé test used for *post hoc* pairwise comparison of hypothesised differences: *$P<0.05$; †$P<0.10$.

Table 5 Multivariate regression models (dependent variable=log of total service cost)

Constant term		Be'er Sheva	Barcelona	Melbourne	Porto Alegre	Seattle	St Petersburg
		8.166 (6.497 to 9.834)	10.566 (9.187 to 11.946)	6.603 (5.557 to 7.649)	5.578 (4.152 to 7.004)	7.394 (6.241 to 8.547)	5.994 (4.293 to 7.696)
Socio-demographic variables							
Age	β	0.003 (−0.014 to 0.021)	−0.0085 (−0.024 to 0.007)	−0.0049 (−0.015 to 0.005)	−0.008 (−0.021 to 0.005)	−0.011* (0.022 to −0.001)	−0.0057 (−0.019 to 0.008)
	Exp (β)	1.003 (0.986 to 1.021)	0.992 (0.976 to 1.007)	0.995 (0.985 to 1.005)	0.992 (0.979 to 1.005)	0.989 (0.978 to 0.999)	0.994 (0.981 to 1.008)
Years of education	β	0.042 (−0.043 to 0.126)	0.0182 (−0.031 to 0.068)	−0.00002 (−0.038 to 0.038)	0.008 (−0.039 to 0.056)	−0.012 (−0.071 to 0.047)	0.0005 (−0.063 to 0.064)
	Exp (β)	1.043 (0.958 to 1.134)	1.018 (0.969 to 1.070)	1.0 (0.963 to 1.039)	1.008 (0.961 to 1.058)	0.988 (0.931 to 1.048)	1.001 (0.939 to 1.066)
Gender	β	0.006 (−0.433 to 0.445)	−0.492* (−0.870 to −0.114)	0.225 (−0.062 to 0.511)	0.531* (0.142 to 0.921)	−0.232 (−0.524 to 0.060)	−0.06 (−0.461 to 0.339)
(0=female; 1=male)	Exp (β)	1.006 (0.648 to 1.561)	0.611 (0.419 to 0.892)	1.252 (0.940 to 1.668)	1.701 (1.153 to 2.511)	0.793 (0.592 to 1.062)	0.941 (0.630 to 1.403)
Marital status (0=single;	β	0.158 (−0.330 to 0.646)	−0.109 (−0.473 to 0.255)	−0.0068 (−0.309 to 0.296)	0.123 (−0.193 to 0.440)	0.066 (−0.205 to 0.336)	0.257 (−0.102 to 0.615)
1=married/other)	Exp (β)	1.171 (0.719 to 1.907)	0.897 (0.623 to 1.290)	0.993 (0.734 to 1.344)	1.131 (0.824 to 1.553)	1.068 (0.815 to 1.399)	1.293 (0.903 to 1.850)
Employment	β	−0.475† (−0.956 to 0.006)	−0.0021 (−0.394 to 0.390)	0.053 (−0.229 to 0.334)	0.296† (−0.043 to 0.635)	−0.152 (−0.464 to 0.159)	0.428* (0.007 to 0.850)
(0=employed; 1=other)	Exp (β)	0.622 (0.384 to 1.006)	0.998 (0.674 to 1.477)	1.054 (0.796 to 1.397)	1.345 (0.958 to 1.887)	0.859 (0.629 to 1.173)	1.535 (1.007 to 2.340)
Clinical variables							
CES to D	β	−0.0008 (−0.025 to 0.023)	0.0036 (−0.016 to 0.023)	0.007 (−0.008 to 0.022)	0.0009 (−0.017 to 0.018)	−0.0017 (−0.017 to 0.014)	−0.007 (−0.028 to 0.013)
	Exp (β)	0.999 (0.976 to 1.023)	1.004 (0.984 to 1.024)	1.007 (0.992 to 1.023)	1.004 (0.984 to 1.019)	0.998 (0.983 to 1.014)	0.993 (0.973 to 1.013)
CIDI status	β	−0.0394 (−0.545 to 0.467)	0.144 (−0.270 to 0.558)	−0.168 (−0.476 to 0.140)	0.418* (0.042 to 0.795)	0.037 (−0.294 to 0.367)	0.163 (−0.224 to 0.551)
	Exp (β)	0.961 (0.580 to 1.594)	1.155 (0.763 to 1.747)	0.845 (0.621 to 1.151)	1.519 (1.043 to 2.214)	1.037 (0.745 to 1.444)	1.177 (0.551 to 1.735)
Comorbid anxiety	β	−0.331 (−1.050 to 0.388)	−0.088 (−0.676 to 0.500)	0.085 (−0.274 to 0.444)	−0.056 (−0.514 to 0.402)	0.390† (−0.008 to 0.789)	0.231 (−0.293 to 0.755)
	Exp (β)	0.718 (0.350 to 1.474)	0.916 (0.509 to 1.648)	1.089 (0.760 to 1.559)	0.946 (0.598 to 1.495)	1.477 (0.992 to 2.200)	1.260 (0.746 to 2.127)
Comorbid alcohol	β	0.342 (−1.383 to 2.066)	0.117 (−0.620 to 0.853)	−0.087 (−0.390 to 0.216)	−0.273 (−0.717 to 0.172)	−0.429* (−0.853 to −0.006)	−0.179 (−1.004 to 0.647)
	Exp (β)	1.407 (0.251 to 7.891)	1.124 (0.538 to 2.348)	0.917 (0.677 to 1.242)	0.761 (0.488 to 1.188)	0.651 (0.426 to 0.994)	0.836 (0.366 to 1.909)
Comorbid chronic	β	0.335 (−0.130 to 0.799)	0.378† (−0.008 to 0.764)	0.210† (−0.097 to 0.517)	0.159 (−0.186 to 0.504)	0.345* (0.039 to 0.652)	−0.161 (−0.612 to 0.290)
medical illness	Exp (β)	1.397 (0.878 to 2.222)	1.459 (0.992 to 2.147)	1.234 (0.907 to 1.677)	1.172 (0.830 to 1.656)	1.412 (0.652 to 1.919)	0.851 (0.542 to 1.336)
SF to 12 physical score	β	−0.0693* (−0.089 to −0.050)	−0.051* (−0.067 to −0.035)	−0.034* (−0.046 to −0.022)	−0.036* (−0.055 to −0.017)	−0.025* (−0.038 to −0.013)	−0.07* (−0.093 to −0.048)
	Exp (β)	0.933 (0.915 to 0.952)	0.950 (0.936 to 0.965)	0.967 (0.955 to 0.978)	0.965 (0.947 to 0.983)	0.975 (0.963 to 0.987)	0.932 (0.911 to 0.953)
R^2		0.210	0.127	0.120	0.107	0.119	0.133
Adjusted R^2		0.182	0.106	0.095	0.080	0.090	0.101
F		7.736*	5.906*	4.894*	3.949*	4.154*	4.170*

CES to D, Center for Epidemiologic Studies – Depression rating scale; CIDI, Composite International Diagnostic Interview; SF–12, 12-item Short Form Health Survey, physical component.
*$P<0.05$.
†$P<0.10$.

Our findings are consistent with earlier studies that showed a strong association between depression and medical or physical comorbidity. For example, an earlier analysis of health care costs among primary care patients with recognised depression in one of the study sites (Seattle) found that on a multiplicative (logarithmic) scale depression was associated with a 50–75% increase in health service costs at all levels of medical comorbidity (Simon *et al*, 1995). A number of studies have also demonstrated the influence of psychiatric comorbidity on the service utilisation rates of people with depression, including an analysis of the US National Co-morbidity Survey, which showed that having a comorbid (alcohol or non-alcohol) disorder was associated with an increased likelihood of service utilisation (Wu *et al*, 1999). In the sampled populations that made up the LIDO study, however, we did not find a consistent trend in terms of the impact of psychiatric comorbidity on costs. This may be attributable in part to the limited measurement of these comorbidities in the present study.

Economic burden of untreated depression in primary care

An important outcome of this research has been the generation of detailed resource utilisation and costs data in a number of culturally diverse primary care settings, based on a common methodology and accompanying protocol. Such data are not only valuable within the national contexts of participating study sites, but are also potentially informative at an international level of comparison. Using purchasing-power parities to convert total health care consumption per subject into US dollars, for example, reveals that the economic burden of currently untreated depression in primary care either approaches or exceeds average per capita health care expenditures (World Health Organization, 2001) in four of the six study sites. This economic burden is substantially increased if the cost of lost work days is also included; 3.7 work days on average (inter-site range: 1.5–8.0) were lost for the total baseline sample in the 3-month period prior to baseline assessment, at a converted cost of $225 per subject. In addition to these whole days of lost work, but not measured here, so-called 'cut-back days' are a further important source of lost productivity in the working population (Kessler & Frank, 1997). These estimates may diverge from that estimated for a population of treated primary care attenders; however, the follow-up of these subjects at 9 months suggests that costs remain quite similar overall (additional depression-specific treatment costs are offset by reduced work days lost and health care consultations), in part because only a modest proportion of subjects received treatment (Simon *et al*, 2002).

Health system disparities and the challenges of cross-cultural health services research

In spite of the consistent methodology used, we see a marked disparity in terms of resource costs associated with health care utilisation and lost work days, most notably in St Petersburg, where a forbidding combination of societal stigma, health system reform, low health professional salaries and financial barriers to access at the user level means that our estimated health care costs are not just relatively but also absolutely low. Such fundamental differences in health system characteristics present a major challenge to multicultural studies that seek to measure the costs or cost-effectiveness of mental health care. In the LIDO study, a deliberate attempt was made to collect data relating to modes of health care financing and provision as well as perceived barriers to access (Chisholm *et al*, 2001*a*). However, the resulting site-level disparity required us to focus more on site-specific rather than pooled analyses, in order to determine whether there were similar cost trends – such as a proportionate increase associated with medical comorbidity – across the six diverse primary care settings. One drawback of such a site-specific analytical strategy is the loss of analytical power that would be available for pooled analyses. Even with samples of more than 300 subjects per site, and despite the magnitude of certain cost differences between the four subgroups, results did not generally reach statistical significance at the 10% level. Such non-significant findings are in part attributable to the fact that all subjects at baseline assessment had depressive symptoms (CES–D > 16), but are also determined by the skewed distribution of resource utilisation rates and costs, which is a common feature of these types of data (Sturm *et al*, 1999).

Cross-sectional analyses such as these have inherent restrictions, notably the absence of follow-up assessment that allow the examination of longitudinal relationships among resource costs, work absences and depression outcomes. Examination of these prospective associations was a further objective of the LIDO study and the results are reported elsewhere (Simon *et al*, 2002). Our hope is that the economic investigations undertaken as part of this observational study collectively lead to improved understanding, over time and across cultures, of the complex interaction among depression symptoms (alone and in combination with other morbidity), economic costs and treatment outcomes. Such insights into the current, largely untreated burden of depression will, we hope, stimulate greater efforts to develop cost-effective, primary-care-based interventions for depressive disorders and their associated comorbidities.

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CLINICAL IMPLICATIONS

- The economic consequences of currently untreated depression in primary care are considerable, both in terms of health care consumption and work days lost.
- Marked disparities in costs were apparent across primary care settings, stemming from differences in health system characteristics including access to and financing of care.
- Medical comorbidity has at least as much influence as symptom severity on the costs of depression.

LIMITATIONS

- The marked health system and cost differences found between participating sites made data pooling inadvisable (with consequent effects on study power).
- Multivariate models of the interrelationship between health care costs, depression status and comorbidity were only able to explain a modest amount of observed cost variation.
- Reported costs relate only to currently untreated depression and therefore may diverge from estimates for treated depression.

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