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Patients with a psychiatric disorder in general practice: determinants of general practitioners' psychological diagnosis

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ABSTRACT

Background: Although psychiatric disorders are highly prevalent in the community, many patients with a psychiatric morbidity remain unidentified as such in primary care.

Objective: The aim of this study was to analyze which clinical and sociodemographic characteristics of patients with psychiatric morbidity are related to general practitioners' (GPs) diagnosis of mental illness.

Methods: A 1-year naturalistic survey of primary care contacts of patients with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnosis of affective disorder, anxiety disorder or alcohol abuse was carried out.

Results: Of the patients with a *DSM-IV* diagnosis, 10% did not visit their GP at all during 1 year, 40% visited their GP but were only diagnosed as having somatic diagnoses and 50% were given a psychological or social diagnosis at least once during 1 year. Affective disorders are more frequently diagnosed than anxiety disorders or alcohol abuse. The chances of psychological GP diagnosis increase with the number of GP contacts.

Conclusions: GPs appear to have few indications to help them distinguish patients with a psychiatric morbidity from others, as long as the patients themselves do not express more explicit clues to their condition. Public mental health education and a better public relations policy are badly needed.

1. INTRODUCTION

Psychiatric disorders are highly prevalent in the community. The 1-year prevalence rates of any psychiatric disorder, measured among more than 60,000 communitydwelling adults between 2001 and 2003 in 14 countries, varied between 4.7% and 26.4% [1], with a 14.9% rate for the Netherlands [2]. Nevertheless, the rates of psychiatric disorders diagnosed in general practice are lower. Lamberts [3], using the International Classification of Primary Care (ICPC) [4], showed a 2.9% prevalence rate of psychiatric diagnoses in 1991. The Second National Survey of General Practice [5] presented a 1-year prevalence rate of 4.7% psychiatric diagnoses using the ICPC.

In this article, we will focus on the characteristics of patients and their psychiatric disorder that may boost their chances of being diagnosed as having psychological or social problems. From earlier research, it is known that female patients and patients well known to their general practitioners (GPs) have a better chance of being recognized as suffering from a mental illness [6,7]. Characteristics of the disorder may play a role as well: depression is better recognized than anxiety disorder [8]; more severe disorders are better recognized than mild forms of psychopathology [8–10]; and physical comorbidity has been reported as both an advantage [11] and a disadvantage [12] with regard to recognition of depression. Psychiatric comorbidity increases the chances of GP recognition of depression [13].

The research question underlying this article is as follows: Which characteristics (sociodemographic, health status, psychopathology) of patients with a *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* diagnosis of depression, anxiety disorder or alcohol

abuse/addiction increase the probability of a GP diagnosis of psychological disorder or social problems?

[FIGURE 1]

2. METHODOLOGY

2.1. Design and patients

The data originate from the Second Dutch National Survey of General Practice. A nationwide, representative sample of 104 general practices participated with 400,000 registered patients (see Fig. 1).

During 1 year, data on all contacts between GPs and patients, including diagnoses, prescribed medications and referrals, were extracted from routine electronic medical records. A random 5% sample of patients was invited to participate in a comprehensive health interview (65% response rate) including two screening instruments. The instruments used were the 12-item version of the General Health Questionnaire (GHQ-12) [14] for general psychopathology and the CAGE Questionnaire [15] for alcohol abuse. Respondents aged 18 years or older with a GHQ score ≥ 4 (subsequently lowered to ≥ 3 to include a sufficient number of patients with psychopathology) and/or a CAGE score of 4 were invited for a standardized psychiatric interview using the Composite International Diagnostic Interview (CIDI) [16]. The CIDI was successfully administered to 811 persons. In this study, we used the computerized Dutch version of the 12-month CIDI (CIDI-Auto 2.1). The following five sections were assessed: demographics; phobic and anxiety disorders; depressive disorders and dysthymic disorders; manic and bipolar disorders; and disorders resulting from the use of alcohol.

CIDI data were combined with data concerning morbidity presented to the GPs by the patients during 1 year around the interview date. This was accomplished for 795 persons, resulting in 6102 doctor-patient contacts for analysis [6 patients had incomplete CIDI data and three practices (with 10 CIDs) were excluded because of incomplete registration during 1 year]. Within a period of 9 months before or after the interview, 90% of the morbidity was presented in contacts, 75% of the data within a period of half a year.

2.2. Nonresponse

The respondents to the health interview (65% response rate) were representative of the general practice population regarding age and sex.

The CIDI respondents did not differ from the nonrespondents regarding age, sex and GHQ score. In the respondent group, those with a higher education level were slightly overrepresented.

2.3. Psychiatric morbidity

CIDI diagnoses indicate psychiatric morbidity during the previous 12 months. By means of diagnostic algorithms, diagnoses according to criteria of the *DSM-IV* were provided. A diagnosis was considered positive when all diagnostic criteria (inclusion as well as exclusion criteria) were fulfilled. Of the 795 respondents to the CIDI, 376 had at least one *DSM-IV* diagnosis. This is the study population we are reporting on.

In our analysis, we distinguished between patients with more and those with less severe psychiatric disorders. More severe disorders included moderate or severe major depressive disorder, bipolar disorder, any recurrent major depressive disorder, panic disorder, compulsive-obsessive disorder and the presence of more than one *DSM-IV* diagnosis. Less severe disorders were single mild major depressive disorder, generalized anxiety disorder, phobia without panic and alcohol abuse.

2.4. Morbidity in general practice

Of all the patients with a *DSM-IV* diagnosis, data about all contacts with their GPs during 1 year were analyzed. During each contact with a patient, a GP registered the diagnosis in an electronic medical record coded according to the ICPC [4]. The ICPC distinguishes separate chapters for psychological symptoms and diagnoses (e.g., depressed feeling, stress or depression, respectively, phobia) and social problems (e.g., family problems, work problems). Separate attention has been given to somatic

symptoms that are considered indicative of depression or anxiety: cold chills, tiredness, sweating, nausea, palpitations, tightness of the chest and lack of appetite. The registration also shows the total number of contacts of each patient during 1 year.

[TABLE 1]

2.5. Patient characteristics collected during the health interview

- A number of demographic characteristics were known for all patients in the survey, from the GP information system or from the survey. These characteristics are presented in detail in Table 4.
- During the health interview, patients assessed their trust in general practice and mental health care on a 10-point scale. They also filled in the number of years they were registered with their GP. During the health interview, patients completed the MOS Short Form (SF-36) as an indicator of functional health status [17]. The subscales are presented in Table 3.

Patients indicated on a list of 30 possible chronic diseases the conditions that they were suffering from. They also indicated the character and number of acute health problems that they had experienced during the last 2 weeks.

Finally, they completed the GHQ-12 (which was also used as the screener to select possible participants for the CIDI).

2.6. Measures

2.6.1. CIDI

The CIDI has been developed for administration by lay interviewers and generates *DSM-IV* diagnoses in psychiatric epidemiological research. In a recent validation study, the CIDI was considered “a highly valid assessment of mental disorders among primary care attendees.” Concordance for CIDI for *International Statistical Classification of Diseases, Tenth Revision* diagnoses was moderate to excellent ($\kappa=.58-.97$) [18].

2.6.2. SF-36

The SF-36 is a 36-item self-report questionnaire yielding scores (0–100) on nine aspects of physical, social and mental functioning. In validation studies of the Dutch version, the internal consistency reliability of the subscales varied from .83 to .92 for a national sample, from .80 to .91 for a migraine sample and from .66 to .90 for a cancer sample. A series of known group comparisons yielded consistent support for the SF-36 [19].

2.6.3. GHQ-12

The GHQ has been developed as a screener for psychiatric disorders in community settings. The 12-item version has been reported to have a sensitivity of .94 and a specificity of .79. The internal consistency of the 12-item version has been reported to vary between .82 and .90; splithalf reliability was shown to be .95 [20].

2.7. Analysis

All patients with at least one *DSM-IV* diagnosis ($N=376$) were selected from the sample interviewed with the CIDI. After these data had been put together with their 1-year general practice morbidity data, the patients were divided into three groups: those with psychopathology according to the CIDI without any contact with their GP ($n=32$), those with psychopathology without any GP diagnosis in ICPC Chapter P (psychological) or Z (social) ($n=151$) and those with psychopathology with at least one GP diagnosis in ICPC Chapter P or Z ($n=193$).

The three groups were compared on the basis of sociodemographic composition, psychopathology (CIDI diagnosis, number of CIDI diagnoses, severity), health status and doctor–patient relationship. This comparison was first conducted at a bivariate level with *t* tests for independent groups (ordinal data with χ^2) and then in a multivariate logistic regression with the inclusion of those variables that

showed significant contributions at a bivariate level. Analyses were performed using SPSS Version 11 for Windows. Significance was accepted at the .05 level.

3. RESULTS

Three hundred seventy-six patients were identified with at least one *DSM-IV* diagnosis of mood disorder, anxiety disorder or alcohol abuse or addiction. Three hundred forty-four had at least one contact with their GP.

[TABLE 2]

[TABLE 3]

(See Table 1 for the distribution of *DSM-IV* diagnoses, as assessed during interview.)

Mood disorders and anxiety disorders were both common among the included patients.

Approximately half of the patients with alcohol disorder or anxiety disorder had a coexistent mood disorder; half of the patients with a mood disorder and one third with alcohol disorder had an anxiety disorder too. Comorbidity is specified in Table 2.

Table 3 presents the diagnoses made by the GPs during 1 year of contact registration.

Approximately half of the patients with a *DSM-IV* diagnosis according to the CIDI were given at least one diagnosis within ICPC Chapter P during 1 year. One quarter were diagnosed as depressed, approximately 13% as being anxious or having an anxiety disorder and 10% as suffering from stress, burnout or neurasthenia. Approximately 10% were diagnosed in Chapter Z (e.g., family problems, working problems and financial problems). Altogether, 193 patients were given a psychological or social diagnosis by their GP during 1 year (with 26 receiving diagnoses from both domains).

Although almost all patients with a *DSM-IV* disorder were given somatic diagnoses as well, 151 only had diagnoses in the somatic chapters of the ICPC. Approximately 20% of all patients received diagnoses of somatic symptoms that are regarded symptomatic for depression or anxiety disorder.

Table 4 gives the patient and symptom characteristics of those given a psychological or social diagnosis by their GP at least once, of those who visited their GP but who never received a psychological or social diagnosis and of those who did not visit their GP.

Patients with psychopathology who were diagnosed by their GP within the psychological or social domain did not differ from patients who were not diagnosed by their GP, as far as their sociodemographic characteristics were concerned. However, significant differences regarding psychopathology characteristics were observed. Among those who received a psychological or social diagnosis was a larger percentage of patients with a psychiatric disorder assessed as severe; there were more patients with a *DSM-IV* diagnosis of mood disorder in this group. In general, there was more psychiatric comorbidity among them than among those without a psychological or social diagnosis (1.47 vs. 1.27 *DSM-IV* disorders). Regarding patients' health status, those who were given a psychological or social diagnosis by their GP had a higher GHQ score (indicating more mental distress), lower mental functioning scores on the SF-36 and far more visits to their GP than those not diagnosed as psychologically ill.

Finally, patients with a psychological or social GP diagnosis tended to express slightly more confidence in their GP. This difference just failed to meet our criterion for statistical significance of .05 (probability being .06).

[TABLE 4]

[TABLE 5]

Compared with patients with psychopathology who did not visit their GP, those from both visiting groups were older, more frequently female, less frequently single and more frequently married. Depression was less frequent among nonvisitors than among patients who were given a psychological

or social diagnosis by their GP. Generally, the health status of the nonvisitors was better: they had fewer chronic conditions and better scores on most of the SF-36 scales.

A multivariate logistic regression analysis was carried out with the psychological or social diagnosis of the GP as the dependent variable to control for intercorrelations between the different significant predictors for a psychological or social diagnosis. Only significant predictors from the bivariate analysis were included in the analysis. Table 5 gives the results.

Controlling for other predictors, patients with a *DSM-IV* depression diagnosis had better chances of receiving a psychological or social diagnosis than patients with an anxiety or alcohol diagnosis. As the number of GP visits increased, the chances of being given a psychological or social diagnosis increased as well. The other predictors that were significant at a bivariate level did not contribute significantly to the prediction of a psychological or social diagnosis anymore, after controlling for the other variables.

4. DISCUSSION

Ninety percent of patients with a *DSM-IV* disorder have primary care contacts during 1 year. Many of them have more than one *DSM-IV* disorder, indicating a highly prevalent psychiatric comorbidity. For instance, approximately half of the patients with an anxiety disorder or substance abuse are depressed as well.

Approximately half of the patients with a *DSM-IV* disorder were given a psychological or social diagnosis by their GP at least once during the year in which the *DSM-IV* diagnosis was assessed. Of those, 10% did not visit their GP during that year and 40% were only given somatic diagnoses. Those 10% without any contact were younger, more frequently single and male; they had fewer chronic conditions and a better functional health status. The odds for being diagnosed by the GP with a psychological or social diagnosis were better for patients with depression than for patients with anxiety disorder or alcohol abuse/ addiction; the odds increased with the number of GP contacts. Chances were also better for patients with more severe psychopathology, more *DSM-IV* diagnoses, a higher GHQ score and more confidence in their GP; however, these effects disappeared after controlling for the former ones.

4.1. Earlier findings

These results are in line with earlier findings. Ormel et al. [8], Tiemens et al. [10], Goldberg and Bridges [21], Joukamaa et al. [22] and Thompson et al. [23] all pointed to the large number of patients with a psychiatric disorder who remained unrecognized by GPs. Coyne et al. [9] and Tiemens et al. [10] corroborate our finding that milder depressions in relatively well-functioning patients are harder to detect. Klinkman et al. [7] stressed the importance of knowing a patient as having a positive effect on recognition. In the same line are Bushnell's [24] results that patients with more contacts are recognized easier as having psychological problems. The large comorbidity between several psychiatric disorders had been described already by Coyne et al. in 1994 [25]. However, these studies were cross-sectional by nature. In most cases, possible mental disorder of a patient was assessed by means of screening questionnaires instead of diagnostic interviews. The current results are based on a more comprehensive foundation in several ways. In our study, psychopathology was not assessed with a screening instrument such as the GHQ but with a thorough standardized diagnostic interview. Moreover, GPs' assessment of the patients' condition was not based on a single encounter but on a comprehensive yearlong registration of all morbidity presented to the GPs. In this way, the often stated advantage of a primary care situation to observe the natural course of illness was used optimally. Nevertheless, the proportion of recognized cases is not higher than usual in these studies.

There might be some other factors that may improve the number of detected cases of psychopathology. GPs with an ability to detect nonverbal signals communicated by the patients are more sensitive for psychological distress [26]. An open and patient-centered communication style has previously been demonstrated to be related to the sensitivity of GPs for mental disorder in other studies [27,28]. On the part of the patients, it has been argued repeatedly that patients should be more ready to communicate their psychological distress. When patients take such initiatives, the number of recognized cases increases [29,30]. Patients who tend to attribute their symptoms to psychological explanations ("I am under a lot of stress these days") have a much higher probability of presenting

with explicit psychological complaints than patients who tend to attribute the same symptoms to normalizing explanations (situational, environmental factors; “This room is much too hot”) [31].

However, variables of this kind are not available in our data set.

4.2. Methodological considerations

In a methodological respect, we should keep in mind that the CIDI provides us with a one-moment recording of psychopathology, literally covering the year before the interview, whereas the GP diagnoses have been collected during 1 year, largely before, partly after the moment of interview. Theoretically, not all consultations with the GPs have fallen within the episode of mental disorder, as assessed by the CIDI. However, given the relatively long duration of an episode of mental disorder, this would have been an exception rather than a rule.

Another observation concerning the methodology has to do with our demarcation between “recognition” and “nonrecognition.” We have defined as *nonrecognition* where a GP has only made somatic diagnoses. Diagnoses within the social domain (often relationship or partner problems) are considered examples of *recognition*. When we draw the line between diagnoses within ICPC Chapter P and all other diagnoses, 13 more patients would remain unrecognized.

A last point of consideration should be the nonresponse. The response rates for both the general health interview and CIDI are satisfactory and are in agreement with the response rates of comparable large-scale health surveys and epidemiological studies, which varied between 62% and 66% [32–34]. Nonresponse at both steps did not have a large impact on the representativeness of our final sample. However, it cannot be denied that ultimately only 38% (.65*.59) of the invited population at risk completed a CIDI. An obvious selection bias might have been an underrepresentation of the nonattendees in our final sample. However, as we were not as much interested in an exact estimation of prevalence but more in an inventory of morbidity presented by patients with a *DSM-IV* diagnosis, our main goal was to include a sufficient number of patients within several *DSM-IV* categories.

5. CONCLUSIONS

5.1. How should these findings be interpreted?

Apparently, quite a lot of people with enough symptoms to meet *DSM-IV* criteria do not put forward explicit demands for psychological help to their GP and in some cases do not even visit their GP during 1 year. The reasons for not making any such demand have been documented in the literature. As Jorm [35] reported, many lay people cannot recognize specific disorders and have incorrect beliefs about the causes and effective treatment of mental illness.

Most patients with a *DSM-IV* disorder do not consider themselves eligible for treatment in any case. Many think that they can handle their problems themselves. Most of those with a perceived need for care, who are in absolute number a minority of patients with a *DSM-IV* diagnosis, prefer not-effective treatment such as information or social support [36]. In general, patients who express a need for treatment prefer counseling far above medication [36–38]. Priest et al. [39] reported the belief among lay people that counseling is far more effective than medication whereas medication was thought by many to be addictive. Given this state of affairs, it is rather predictable that many patients with psychological problems are not inclined to put forward a demand for help to their GP, because they might expect a treatment with medication rather than counseling or another form of therapy.

Within such a context, it is not surprising that a relatively large proportion of approximately 40% of visiting patients with a *DSM-IV* diagnosis are not diagnosed as such by a GP. Apparently, many of them did not seek help for psychological problems. It does not seem reasonable to assign GPs the task of detecting psychological problems when patients do not seek help for them and rather often do not exhibit the typical symptoms of, for example, depression or anxiety.

Solutions might be sought in better demonstrations of the benefits of therapies for psychological problems, which, if convincing, might be of great benefit to the mental health education of the public. For the relatively large proportion of undetected psychiatric morbidity, there appears to be a public relations problem, at least to some extent.

6. CLINICAL IMPLICATIONS

- GPs should be aware of the fact that patients with a psychiatric disorder are not likely to ask explicitly for help for their psychological problems.
- The public should be better informed about the treatment possibilities of mental disorder in primary care.

7. LIMITATIONS OF THE STUDY

- No exact match in time framework between CIDI (diagnosis concerning 1 year before the interview) and GP registration (1-year registration around the interview date).
- No datum available about patients' reasons for their GP visits (only GP diagnoses).

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TABLES AND FIGURES

National Study: 400,000 patients enlisted. 1-year morbidity registration by GP
↓
5% sample health interview: 19,685 patients eligible
↓
65% response: 12,699 respondents
↓
GHQ/CAGE positive: 1379; invitation CIDI
↓
811 CIDI completed (59% response)
↓
795 CIDI completed + 1 year morbidity data available
↓
376 patients with a DSM-IV disorder + 1 year morbidity available

Fig. 1. Flowchart of data collection.

Table 1
 Specific diagnoses of respondents with at least one *DSM-IV* diagnosis (*N*=376)

Diagnosis	<i>n</i> (%)
Alcohol disorder	41 (11)
Mood disorder ^a	247 (66)
Major depressive disorder single mild	96 (26)
Major depressive disorder single moderate	67 (18)
Major depressive disorder single severe	52 (14)
Major depressive disorder recurrent mild	15 (4)
Major depressive disorder recurrent moderate	6 (2)
Major depressive disorder recurrent severe	3 (1)
Dysthymia	41 (11)
Bipolar disorder	8 (2)
Anxiety disorder ^b	232 (62)
Panic disorder without agoraphobia	18 (5)
Panic disorder with agoraphobia	20 (5)
Agoraphobia without panic disorder	49 (13)
Social phobia	52 (14)
Generalized anxiety disorder	113 (30)
Specific phobia	113 (30)

^a Different depressive disorders are mutually exclusive, except for dysthymia.

^b Different anxiety disorders are not mutually exclusive.

Table 2
 Comorbidity among respondents with at least one *DSM-IV* diagnosis (*N*=376)

CIDI comorbidity	Alcohol (<i>n</i> =41)	Mood disorder (<i>n</i> =247)	Anxiety disorder (<i>n</i> =232)
Alcohol [<i>n</i> (%)]	41 (100)	19 (8)	12 (5)
Mood disorder [<i>n</i> (%)]	20 (49)	247 (100)	126 (54)
Anxiety disorder [<i>n</i> (%)]	12 (29)	122 (49)	232 (100)

Table 3
 GP diagnoses for patients with any *DSM-IV* disorder (*N*=376)

No GP contact	32
No. of those with at least one contact [<i>n</i> (%)]	344 (100)
Any psychological symptom/diagnosis (P) [<i>n</i> (%)]	180 (52)
Alcohol (P15) [<i>n</i> (%)]	2 (0.6)
Depression (P03/P76) [<i>n</i> (%)]	78 (23)
Anxiety (P01/P74) [<i>n</i> (%)]	46 (13)
Stress/surmenage (P02/P78) [<i>n</i> (%)]	37 (11)
Affective psychosis (P72) [<i>n</i> (%)]	3 (0.8)
Social problem (Z) [<i>n</i> (%)]	39 (11)
Somatic symptom anxiety (A02, A04, A09, D09, K04, R02) ^a [<i>n</i> (%)]	48 (14)
Somatic symptom depression (A04, T08) ^b [<i>n</i> (%)]	27 (8)
Any somatic symptom [<i>n</i> (%)]	331 (96)

^a Includes cold chills, tiredness, abundant transpiration, nausea, palpitations and tightness of the chest.

^b Includes tiredness and lack of appetite.

Table 5
 Logistic regression on psychological or social diagnosis versus only somatic diagnosis

Predictors	β	<i>P</i>	Odds ratio	95% Confidence interval
<i>DSM-IV</i> depression	.93	.004	2.55	4.77–1.35
Severity	.71	.059	2.04	0.97–4.26
No. of <i>DSM-IV</i> diagnoses	.62	.043	1.86	1.02–3.39
GHQ score	.079	.137	1.08	0.98–1.20
No. of GP visits in 1 year	.095	.000	1.10	1.06–1.15
SF-36 mental functioning	-.006	.421	0.994	0.98–1.01

Table 4
 Patient characteristics and recognition of mental disorder

	Psychological/ social diagnosis (n = 193)	Only somatic diagnoses (n = 151)	No visit to GP during 1 year (n = 32)
Sociodemographic characteristics			
Age (years)	45 ^a	45 ^b	38 ^{a,b}
Sex (% men)	35 ^b	27 ^a	53 ^{a,b}
Education (%)			
Low	17	15	9
Middle	62	62	69
High	22	23	22
Marital status (%)			
Single	31 ^b	33 ^b	53 ^b
Married	49	57	34
Divorced	13	5	9
Widowed	7	5	3
Insurance (%)			
Public	72	72	74
Private	28	28	26
Disorder characteristics (%)			
DSM-IV depression	75 ^{b,c}	56 ^c	56 ^b
DSM-IV anxiety	62	62	63
DSM-IV alcohol	10	10	19
Severe DSM-IV disorders	60 ^a	44 ^a	50
No. of DSM-IV diagnoses	1.47 ^c	1.27 ^c	—
Presenting somatic symptoms anxiety	26	16	—
Presenting somatic symptoms depression	12	8	—
Health status			
GHQ score	7.1 ^a	6.2 ^a	6.3
No. of chronic conditions	2.3 ^a	2.6 ^b	1.3 ^{a,b}
No. of acute complaints	9.4	8.9	9.8
No. of GP visits in 1 year	10.9 ^c	6.8 ^c	0 ^c
Functional status (SF-36)			
Physical functioning	77 ^b	76.5 ^b	88.1 ^b
Social functioning	63.1 ^b	65.2	76.6 ^b
Physical role	51.0	47.8	50.0
Emotional role	45.6	48.6	57.3
Mental functioning	49.2 ^{a,b}	55.8 ^a	57.0 ^b
Vitality	41.3 ^b	43.6	49.5 ^b
Pain	54.1	52.5	54.5
General health	50.3 ^a	52.1	60.6 ^a
Changes in health	47.5	46.9	49.2
Doctor-patient relationship			
Confidence in GP (1 = much, 4 = little)	2.0	2.1	2.1
Confidence in mental health care	2.8	2.9	2.7
Years enlisted with GP	13.6	15.9	11.2

Differences have been assessed by *t* tests for independent groups.

^a Significant difference with first, second or third column ($P < .01$).

^b Significant difference with first, second or third column ($P < .05$).

^c Significant difference with first, second or third column ($P < .001$).

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