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Characteristics of subjects with comorbidity of symptoms of generalized anxiety and major depressive disorders and the corresponding threshold and subthreshold conditions in an Arab general population sample

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Background:

Summary

There is controversy about differential meaningfulness between comorbid generalized anxiety disorder (GAD)/ major depressive disorder (MDD), the corresponding "pure" disorders and sub-threshold conditions. We compared subjects who met DSM-IV^{TR} criteria of symptoms and functional impairment for comorbid GAD/MDD, versus those with GAD, MDD, subthreshold conditions, and without significant symptoms. The comparison measures were socio-demographics, clinical severity, and quality of life (QOL).

Material/Methods:

Participants (N=3155: 55.1% female, aged 16–87 yrs) were a general population sample of Kuwaitis who self-completed DSM-IV^{TR} criteria-based questionnaires and the WHOQOL-BREF in 2006/7. We scrutinized the questionnaires and classified them into categories.

Results:

Of the 273 GAD and 210 MDD cases, the prevalence of comorbidity among cases with GAD was 30.8%, and 40% among MDD. Of the 398 subthreshold GAD and 194 subthreshold MDD cases, 58 had subthreshold anxiety/depression comorbidity. Comorbid threshold GAD/MDD cases were significantly older, and more likely to be women, divorced and unemployed, compared with GAD and MDD. In all measures, the threshold GAD/MDD comorbidity was the severest condition. There was a monotonic decrease in QOL with increasing anxiety-depression symptoms. For the predictors of subjective QOL, the GAD/MDD comorbidity group differed markedly from the others.

Conclusions:

The high prevalence of comorbidity and subthreshold conditions supports the recommendation to assess them routinely, regardless of the primary reason for consultation. Our findings support a dimensional model with comorbid GAD/MDD at the higher end of a continuum, and differing from the "pure" conditions by a later onset and predictors of subjective wellbeing.

Key words:

comorbidity • anxiety • depression • subthreshold

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BACKGROUND

Psychiatric comorbidity is defined as consisting of both the co-occurrence of 2 or more specific disorders in an individual in a given period of time [1,2], and the possibility that the disorders could be correlated or co-vary in a group of people [3]. Despite the large body of work on the comorbidity of generalized anxiety disorder (GAD) and major depressive disorder (MDD) [4–11], as well as the corresponding threshold (or “pure”) and subthreshold conditions [2,12–15], controversy persists about the differences in characteristics between subjects with these conditions [16–19]. The controversy is epitomized by the debate on how to classify these disorders in the forthcoming American DSM-V and the WHO ICD-11 [20]. These conditions are important because they are highly prevalent mental disorders in general population [21–23] and clinical samples [24,25], and are associated with significant functional impairment and psychosocial burden [6,26,27]. Furthermore, MDD has comorbidity with subthreshold anxiety, while GAD has comorbidity with subthreshold forms of depression, the high prevalence of which may contribute to comparable economic burden with the “pure” disorders [13,28]. Even relatively mild psychological distress, as in subthreshold forms, may be associated with more long-term psychosocial disability than previously acknowledged [29].

It is important to inquire into the differences in characteristics between subjects with these conditions because of the controversy over the nature of the disorders. The research question is whether there is differentiating meaningfulness between comorbid threshold GAD/MDD on the one hand, and GAD, MDD, and comorbid subthreshold mixed anxiety-depressive disorder (MADD) on the other hand [17,18]. In other words, are these disorders discrete entities or do they indicate a liability (ie, underlying) continuum [3,30]? While the consensus of opinion is that comorbid threshold GAD/MDD is highly prevalent and is a more severe condition than either of the corresponding “pure” disorders, in terms of all measures of distress and disability [4,6,26], some authors indicated that the differences are quantitative, not qualitative [2,31]. On the other hand, an impressive body of data indicates that comorbid threshold anxiety/depression may be a distinct disorder that shares important latent psychological and genetic characteristics with the “pure” disorders [1,3,16,18]. Impressed by the evidence, Tyrer [32,33] has called for the introduction into psychiatric nosology of an entity called “cothymia”, consisting of comorbid threshold anxiety/depression. First, anxiety/depression comorbidity occurs more frequently than would be expected by the base rates of the corresponding “pure” disorders in the population [3,34]. Comorbidity occurs both for methodological reasons (ie, there are shared diagnostic criteria) and substantive reasons (ie, one disorder causes the other) [35,36]. Second, there are indications that the risk factor profiles for comorbid anxiety/depression (eg, socio-demographics, clinical severity, family history, social adversities and quality of life) differ significantly from those of the pure disorders [1,17,18]. Hence, comorbidity is said to be more than the sum of its parts [4]. Third, comorbidity is predicted by the tripartite model of anxiety and depression [37] and the related hierarchical statistical models [3,38,39]. Fourth, in a study of HPA axis function and CNS adrenergic function, it was found that pure anxiety

was associated with noradrenergic abnormality, pure depression was associated with a disruption of the normal negative correlation between the 2 systems, and, notably, hyperactivity of the HPA axis was uniquely associated with the comorbid state [4]. It was concluded that this was an indication that there is something qualitatively (not just quantitatively) distinct biologically about the comorbid state. Finally, findings of studies that combined statistical modeling with the results of genetic studies support a hierarchical conceptualization of psychopathology [3] whereby GAD and MDD are linked to broad psychological factors (eg, neuroticism, internalizing factors), and at the genetic level their liabilities are at once strongly correlated and contain distinguishing features. Hence, GAD/MDD comorbidity is neither a chance occurrence, nor is it indicative of an independent dimension [3,30,40]. In addition, patients with subthreshold conditions had disorders that reflected milder manifestations of the same underlying genetic liability as those with fully syndromal disorders [40].

The situation is further complicated by the controversy over the nature of the corresponding subthreshold disorders. First, there is a problem of nomenclature, with the terms “subthreshold”, “subsyndromal” and “subclinical” being used in different ways. For example, in a review of 36 studies, 25 of them did not include the idea of significant clinical impairment in their definition of subthreshold disorders [15]; but this yardstick is crucial in the DSM-IV (appendix section) concept of subthreshold MADD, and the recognition of subthreshold GAD as “anxiety disorder not otherwise specified” (Anx NOS) [14,41]. Second, there are indications that depression is a clinically homogeneous illness, in which symptoms of major and subthreshold disorders commonly alternate as different manifestations and levels of illness activity in an individual [12,13,28,42]. However, reviewers [13,15] have clarified the definition of these subthreshold disorders using the example of depression in DSM-IV^{TR}, thus: (a) “Subthreshold” refers to cases with less than the required 5 symptoms, the symptoms include depressed mood and loss of interest in usual activities, and there is significant functional impairment. This is equivalent to “depression not otherwise specified” (DNOS) of DSM, consisting of “minor depression”, brief recurrent depression and dysthymia; (b) “Subsyndromal” refers to cases in which there are less than 5 symptoms, which do not include depressed mood and loss of interest, but there is significant clinical impairment; (c) “Subclinical” refers to cases with no significant functional impairment; and (d) “mixed anxiety-depressive disorder” (MADD) as defined in the ICD-10 and appendix of the DSM, namely, cases with co-occurrence of subthreshold depression and anxiety, in the presence of clinically significant functional impairment. The characterization of subthreshold disorders presents a more accurate burden of anxiety/depression morbidity in the population [15,43].

The above highlighted issues regarding anxiety/depression comorbidity have not been investigated using samples from the Arab world. Interest in comorbidity in Arab countries concerned the prevalence of co-occurrence of chronic physical illnesses (eg, diabetes mellitus and hypertension) and significant symptoms of anxiety and depression among primary health care attendees in Qatar and the UAE [44,45]. In the Arabian Gulf country of UAE, it was estimated that

about 20% of sub-threshold cases did manifest full clinical symptoms after 1 year [46]. In the larger world, there is a paucity of general population studies that have simultaneously compared a broad range of groups, consisting of subjects with comorbid threshold GAD/MDD on the one hand, versus subjects with MDD, GAD, MADD, subthreshold conditions, and those without significant symptoms of psychopathology, on the other hand [47]. The use of general population samples to investigate the issues of comorbidity avoids the selection bias inherent in clinical samples [11,35]. This is because the non-restriction of subjects means that all levels of severity of depression and anxiety are represented [18]. Furthermore, the use of symptom-level data has the potential to expose greater variation in the data than do disorder-level variables [48].

The general aim of our study was to contribute to the understanding of the characteristics of subjects with symptoms of comorbid threshold GAD/MDD, using a general population sample from a non-Western country. This is in view of the fact that, apart from the World Mental Health Survey reports, which included data from the developing countries [7,22], virtually all the available literature on this topic emanates from North America and Western Europe. The specific objectives were to compare subjects who met DSM-IV^{TR} criteria of symptoms and functional impairment for comorbid GAD/MDD, versus those with GAD and MDD, as well as those with comorbid subthreshold anxiety/depression (ie, mixed anxiety-depression: MADD), subthreshold depression (ie, DSM-IV: minor depression), subthreshold anxiety (ie, DSM-IV: Anx NOS), and subjects without significant symptoms of anxiety and depression. The comparison measures were: socio-demographic characteristics, symptom profiles, functional impairment, clinical severity, perceived need for psychological/medical assistance, profile of subjective quality of life (QOL) and predictors of QOL. By examining the symptom profiles, we hoped to see whether the comorbid threshold GAD/MDD group was significantly better characterized by a set of symptoms, compared with the other psychopathology groups. We included perceived need for psychological/medical assistance as a measure of severity because it has been shown to be significantly associated with perceived severity of symptoms [22,49,50]. We note that, with respect to our data, while measures such as age, unique symptoms and predictors of QOL deal with possible qualitative differences between the groups, the other measures concern quantitative differences. Based on the literature reviewed above, we hypothesized that subjects with symptoms of comorbid threshold GAD/MDD would differ from those with only GAD or MDD by socio-demographic characteristics, would have significantly more severe symptoms and functional disability, and the QOL domain representing subjective wellbeing would have uniquely different predictors in regression analyses.

MATERIAL AND METHODS

Subjects and setting

Of the total 3.4 million population, Kuwaiti nationals make up 1.1 million (51.1% female) (2007 census). The adult literacy rate in Arabic is very high (83.5% by 2003 estimate); so that, for practical purposes, any Kuwaiti adult that is not mentally challenged can self-complete simple questionnaires

in Arabic. Administratively, the country is divided into 6 governorates or districts, each consisting of a centrally located large cooperative supermarket store, as well as municipal government offices and an immigration office. Our sampling framework was the 6 governorates, and participants were recruited at the above locations.

Our method of sampling was aimed at recruiting a large number of subjects in the general population with symptoms of the disorders of interest. We emphasize that this was not a study of the prevalence rate of mental disorders in the general population. In other words, our objectives did not require a probability sample.

Of the 3376 subjects who agreed to participate in the study, 73 questionnaires were voided because subjects did not complete over 20% of the items of the WHOQOL-BREF, as recommended by the WHOQOL Group [51]. Of the remaining 3303 subjects, we could not use the data for 148 because of missing items in the GAD and MDD questionnaires (details below). Hence, we report the data for 3155 subjects. The 3155 participants (44.9% men, 55.1% women) were aged 16–87 (mean 35.5, *SD* 12.1) years. Similar to the Kuwaiti national general population, women were in the majority and 2.4% of the subjects were aged 65 and above. The subjects were literate in Arabic (59.7% had at least college education), were predominantly employed in skilled work (58.4%), and were married (60.8%). They self-completed the Arabic versions of the questionnaires at the study locations.

Instruments

1. To assess MDD and GAD, we used the Arabic translation of 2 self-rated screening instruments that are based on the DSM-IV^{TR} criteria, viz: (i) the 9-item MDD version of the Primary Care Evaluation of Mental Disorders (the PHQ-9) [52,53]; and (ii) a similarly framed 8-item questionnaire (GAD-S) for assessing GAD, originally articulated by Seitz [54] as a mnemonic for understanding the symptoms of GAD. The psychometric properties (reliability and validity) of these 2 instruments have been shown to be highly satisfactory in the Kuwaiti general population [38]. This was ascertained by test-retest reliability over a 1-week interval (intra-class correlation coefficient: PHQ-9: 0.86; GAD-S: 0.89); item-internal consistency; item-discriminant validity; internal consistency; floor/ceiling effects; factor analysis; and confirmatory factor analysis.

We have used disorder-specific screening instruments based on the DSM-IV criteria, because those criteria incorporate the 3 planks on which psychiatric diagnoses are based in the ICD-10 and DSM-IV, after excluding disorders that could account for the symptoms. The 3 planks are: the presence of a sufficient number and severity of symptoms characteristic of the disorder (ie, the requirement of distress); the presence of sufficient duration of the distressing symptoms (ie, the requirement of durability); and the presence of perceived disability in psychosocial functioning resulting from the symptoms (ie, disability) [41]. Hence, instruments based on these criteria have diagnostic advantage over the older anxiety – and depression – screening instruments [55,56]. This is because, by a scrutiny of each completed questionnaire, they can be used to diagnose MDD and GAD by applying DSM-IV/ ICD-10 diagnostic algorithms to respondents' self-reports [24,56–58].

The MDD and GAD scales

PHQ-9

Although the PHQ-9 was originally designed for use in primary care settings, it has been found to be reliable and valid in general population studies [59–61]. For each item of the PHQ-9 (which correspond with the DSM-IV^{TR} items), respondents indicated whether during the past 2 weeks the symptom had bothered them: “not at all”, “several days”, “more than half the days”, or “nearly everyday”. An item at the end of the questionnaire asked the respondent if he or she had checked off any of the problems in the questionnaire: “how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?” The response options were: “no difficulty”, “mild difficulty”, “moderate difficulty”, and “severe difficulty”.

The internal consistency (Cronbach’s alpha) for the responses of the 3155 participants was 0.86 (split-half reliability: 0.75)

GAD-S

Of the available diagnostic criteria-based screening instruments for GAD [62], we preferred the one by Seitz [54], for the following reasons. First, it is the only one that restricted itself to all the 8 item-symptoms of the DSM-IV, with the screening questions being directly derived from the wordings of the DSM-IV. Second, it has an item for duration of symptoms. Third, a similar measure, the GAD-7 [63,64], which assesses GAD symptoms and worry, has been criticized as prioritizing brevity over comprehensiveness [65]. Fourth, another similar measure that sought this comprehensiveness (GAD Questionnaire for the DSM-IV: GAD-Q-IV) [66] was framed using a somewhat complex scoring system [65] that we considered to be difficult for our subjects if it were to be self-administered in a general population setting.

In order to bring the GAD-S in line with the more detailed section of anxiety as in the PHQ (ie, section 5 of the full PHQ – [52]), subjects were requested to state how much they had been bothered by any of the symptoms in the last 4 weeks, with the following response options: “not at all”, “several days”, or “more than half the days”. In the second part of the questionnaire, the subject is requested to state the duration of the symptoms: “not at all”, “1–2 months”, “3–5 months”, and “6 months and above”. They were also requested to rate the level of functional disability associated with the anxiety symptoms (as detailed above for MDD). The internal consistency (Cronbach’s alpha) for the responses of the 3155 participants was 0.83 (split-half reliability: 0.78).

Diagnosing GAD and MDD

Following the method of a Nordic study in which self-ratings of DSM-IV criteria-based instruments were analyzed to diagnose GAD and MDD [24], we manually scrutinized each completed questionnaire to sort subjects into categories of: (i) GAD; (ii) MDD; (iii) comorbid threshold GAD/MDD; (iv) subthreshold GAD (i.e., DSM-IV: Anx NOS); (v) subthreshold MDD (ie, DSM-IV: “minor depression”); (vi) comorbid subthreshold anxiety/depression (ie, DSM-IV appendix: “mixed anxiety and depression” – MADD); and

(vii) those without clinically significant symptoms of anxiety and depression.

Guided by the DSM-IV^{TR}, to qualify for a diagnosis of MDD we required the following: (a) That the subject should have the simultaneous presence of “depressed mood” and “loss of interest/pleasure in usual activities”, at severe levels (ie, “more than half the days”, or “nearly every day”); (b) Of the remaining 7 items, at least 3 items must be positive at the level of “more than half the days”; (c) then, as recommended by the authors of the PHQ-9 [52], any positive level for the disability item.

Also in line with the DSM-IV^{TR} criteria for “minor depression” and the recommendations of the authors of the PHQ-9, we defined sub-threshold MDD, thus:

Sub-threshold MDD differed from full MDD by the presence of a total of 2 to 4 symptoms (instead of 5). The items included depressed mood and loss of interest, and the presence of the disability item [13,15]. However, subjects positive for 5 or more items were also included in this category if none of the items on depressed mood and loss of interest were experienced on “more than half the days”, and other items were positive for only “several days”. In other words, the sub-threshold cases all admitted having some prominent symptoms with the presence of functional disability. All other subjects were classified as “screen negative”.

For a diagnosis of GAD, we were mindful of the DSM-IV^{TR} requirement of 5 items (including excessive anxiety/worry and difficulty controlling it), at a severe level (ie, “symptoms present for more days than not”), duration of 6 months and some level of functional disability [67]. In view of the noted limitations of the PHQ [68], we sought to define “excessive worry” rigorously, thus: The subject was required to respond to the anxiety/worry symptom at the level of “more than half the days”, and also the next item on difficulty in controlling the worry, at the level of “several days” or “more than half the days”. In other words, we required not only the presence of the principal anxiety symptom at the severest level, but also a severe degree of difficulty with controlling the symptom [67]. Thereafter, the presence of 3 more symptoms was required. Furthermore, the subject should have been experiencing the symptoms for at least 6 months and indicate a level of psychosocial disability.

In view of the controversy over the classification of subjects who fulfilled the symptom- and disability- criteria for GAD, but had duration of symptoms less than 6 months [69,70], data for such subjects (N=96 of 3303: 2.9%) were not used for this analysis. Also not included in this analysis were data for subjects to whom we could not assign a diagnosis because they did not indicate any level of disability, despite having sufficient symptoms for either GAD or MDD (N=52 of 3303: 1.6%).

In line with the DSM-IV^{TR} category of Anx NOS, the sub-threshold level of GAD was defined as follows:

Sub-threshold GAD: the presence of 2 to 4 symptoms (including anxiety/worry and difficulty with controlling worry), at any level of severity, plus any indicated duration of symptoms [69], plus the disability item. All other subjects

Table 1. Differences in socio-demographics for subjects with grades of anxiety/depression, and no anxiety/depression.

Diagnostic group	N	Gender: Females %	Mean age (SD) [95% C.I.]	Marital status % divorced	Educational status % college education	Occupational status % unemployed
Only MDD	78	62.9	31.1(10.4) [28.8–33.5]*	6.5**	50.0	13.0
Only GAD	153	59.5	32.7(10.8) [30.9–34.4]*	9.2**	59.9	8.6
Comorbid MDD/GAD	84	67.9	36.1(12.9) [35.3–38.9]*	20.2**	51.2	17.9
MDD comorbid subthreshold GAD	48	56.3	38.6(14.6) [34.4–42.9]	29.2	44.7	29.2
GAD comorbid subthreshold MDD	36	75.0	34.9(13.1) [30.5–39.4]	25.0	63.9	17.1
Comorbid subthreshold MDD/GAD	58	58.6	35.5(11.9) [32.3–38.6]	15.5	63.8	17.2
Only subthreshold GAD	292	56.2	36.2(13.1) [34.7–37.7]	10.3	54.0	14.2
Only subthreshold MDD	100	62.0	37.8(13.3) [35.2–40.4]	21.0	47.4	23.7
No GAD/ MDD	2306	53.0	35.6(11.9) [35.1–36.0]	8.7	61.7	11.9
All subjects	3155	55.1	35.5(12.1) [35.1–35.9]	10.2	59.7	12.9
Statistics		$\chi^2=25.1$ $Df=8$ $P<0.0001$	$F=3.38$, $df=8/3149$ $P<0.001$	$\chi^2=64.7$ $Df=16$ $P<0.0001$	$\chi^2=34.2$, $Df=16$ $P<0.005$	$\chi^2=60.4$ $Df=32$ $P<0.002$

* Those with MDD/GAD comorbidity were significantly older than those with only MDD ($t=2.7$, $df=160$, $P<0.008$), and those with only GAD ($t=2.1$, $df=235$, $P<0.03$); ** Those with MDD/GAD comorbidity were significantly more likely to be divorced than those with only MDD ($\chi^2=5.3$ $df=1$, $P<0.02$), and those with only GAD ($\chi^2=4.8$, $df=1$, $P<0.03$).

were regarded as anxiety screen negative [14]. We also identified subjects with GAD with comorbid subthreshold depression, and those with MDD comorbid subthreshold anxiety. In summary, the categories of subjects for comparison are shown in Table 1.

We sought to minimize the issues of reliability and validity of this methodology by making stringent definition of symptoms, by strictly following an algorithm based on DSM-IV criteria, and by jointly agreeing on all cases. For example, in view of the fact that the definition of subthreshold conditions may be regarded as imprecise [20,28], our operational definitions all corresponded with the DSM-IV^{TR}. Accordingly, in line with the findings of the DSM-IV field trials [71], we found that, in practice, the subthreshold cases rarely reported experiencing symptoms “nearly everyday” or “more days than not”.

The WHOQOL-BREF

Subjective QOL was assessed with the World Health Organization’s WHOQOL-BREF [51]. The psychometric properties (reliability and validity) of the WHOQOL-BREF have been shown to be highly satisfactory in the Kuwaiti general population [72] and another Arab country [73].

This is a 26-item self-administered generic questionnaire, being a short version of the WHOQOL-100 scale [51]. The response options range from 1 (very dissatisfied/very poor) to 5 (very satisfied/very good). Assessments are made over

the preceding 2 weeks. It consists of domains and facets (or sub-domains). The items on “overall rating of QOL” (OQOL) and subjective satisfaction with health constitute the general facet on OQOL and health.

The more popular model for interpreting the scores has 4 domains: physical health (7 items), psychological health (6 items), social relations (3 items) and environment (8 items). The domain scores used for this presentation were computed by transforming the raw scores onto a 0–100% scale [74]. The internal consistency (Cronbach’s alpha) value for the entire population of subjects was 0.93.

In search of qualitative distinguishing features between the psychopathology groups, we hypothesized that if comorbid threshold GAD/MDD is distinct from the “pure” disorders there would be marked differences (in comparison with the other groups) in the set of predictors of that aspect of the WHOQOL-BREF that most represents subjective wellbeing (ie, the general facet). Theorists regard subjective wellbeing as the core construct of subjective QOL [75,76], which is what the WHOQOL-BREF addresses [77]. To test this hypothesis in multiple regression analyses, we used the general facet as the dependent variable. This is because, unlike other aspects of QOL that are thought to be either health-related (eg, physical/psychological health) or contextual (eg, social relations/environment domain) [77], subjective wellbeing is thought to have a biological/physiological equivalent that is inherent in human homeostasis – just like thermoregulation [76]. In support of this theory, there

is an emerging impression that genetic mechanisms are involved in a broad range of human functions, including subjective experiences such as symptoms of patient-reported outcomes and QOL [78–80].

Indices of functional health status

The items on current feeling of illness and somatic complaints were the exact items in the introductory section of the WHOQOL-BREF. The items on pain and negative feelings were items 3 and 26 of the WHOQOL-BREF. The items on functional disability and suicidal ideation were from the PHQ-9. We chose the PHQ-9 framing of suicidal ideation because it suits the cultural sanctions against suicidal behavior in our setting.

Perceived need for psychological services (“unmet need for care”) [50] among those with MDD and GAD was assessed by their response to an item on whether they felt they needed psychological assistance from any sources (response options: “no problem”, “need help only from friends”, “need medical/psychological help but not receiving it”, “need medical/psychological help and receiving it”) [81].

Procedure

The study took place in 2006–2007. The questionnaires were translated into Arabic by the method of back-translation. Thereafter, we presented the questionnaires to senior Arab medical doctors and psychologists for comments. Ethical approval was obtained from Kuwait University and the Kuwait Foundation for the Advancement of Science (KFAS). We obtained permission from the authorities of each study location to interview Kuwaiti nationals attending their facility. All participants gave verbal informed consent.

The staff of a professional social research company was responsible for circulating and retrieving the questionnaires. These research assistants (RAs) were all Kuwaiti nationals who had previously undergone a 2-month course on research methods and interview techniques at Kuwait University. To recruit prospective respondents, the RAs were positioned at the main entrance of the place and introduced themselves as Kuwaitis doing a study, politely explained the objectives of the study, requested consent to participate, and the subject was informed that no penalty would result from declining to participate.

At the preliminary stage of the study, the RAs were trained in use of the study’s questionnaires in a 1-week period. We did not compute inter-rater reliability because the questionnaires were all self-administered. Only subjects literate in Arabic were invited to participate. In all cases, the participants completed the questionnaires anonymously and privately at the study locations. The RAs were nearby to offer assistance in clarifying the items.

Test-retest reliability was done by giving the questionnaires twice in a 1-week period to 50 subjects who did not participate in the main study.

Data analysis

Data were analyzed by SPSS version 15 [SPSS Inc, Chicago, IL]. We scrutinized all the questionnaires manually and

jointly agreed on the diagnostic category of each respondent based on the criteria previously highlighted.

The characteristics of subjects with comorbid threshold GAD/MDD were compared with those of other categories described above. Following the distinguishing characteristics (or validators/outcome measures) used by other workers [1,17,43], we compared the subjects using the following measures: (i) socio-demographics (sex, age, education, occupation and marital status – Table 1); (ii) prevalence of poor functional health status (non-specific complain of feeling ill, severe functional disability, severe suicidal ideation, somatic complaints, severe feeling of pain, severe negative feelings; and perceived need for formal psychological assistance – Table 2); (iii) clinical severity (frequency distribution of GAD and MDD items, scores on anxiety, depression, and subjective QOL – Tables 3–5); and (iv) QOL: profile of predictors of subjective wellbeing (general facet) [82].

Since age and total scores on anxiety, depression and QOL domain scores were fairly normally distributed, we assessed significant differences between groups by one-way ANOVA. Chi-square tests were used to assess significant differences between groups for categorical variables. Since age and scores on anxiety and depression were significantly correlated with QOL domain scores, differences in QOL domain scores across the groups were re-analyzed by ANCOVA, with age, anxiety and depression scores as covariates. Step-wise regression analysis was used to assess the differences in profile of predictors of QOL for the various groups. Based on previous experience [83], the variables were entered in the following steps: step 1 – age and sex; step 2 – education, marital and occupational status; step 3 – clinical/functional impairment (pain, suicidal ideation, etc); step 4 – anxiety score; and step 5 – depression score. Multi-collinearity was assessed by the values of “tolerance” (cut-off score ≤ 0.2) and variance inflation factor (VIF – cut-off score > 4.0) [84]. Missing data were handled by excluding cases analysis-by-analysis. The level of statistical significance was set at 5%, and all tests were 2-tailed.

RESULTS

Diagnostic groups (Table 1)

As explained above, we are reporting data on 3155 subjects (95.5% of 3303) because, of the 3303 who had usable data for the QOL analysis, 148 could not be used for the comorbidity analysis owing to missing data. Of the 3155, 210 (6.7%) fulfilled the criteria for MDD, while 273 (8.7%) fulfilled the criteria for GAD. Of the GAD and MDD cases, 84 had threshold GAD/MDD comorbidity. Hence, the prevalence of threshold comorbidity among cases with GAD (ie, MDD co-occurring in subjects with GAD) was 30.8% (84/273). The prevalence of threshold comorbidity among cases with MDD (ie, GAD co-occurring in subjects with MDD) was 40% (84/210). Hence, the odds of GAD co-occurring in MDD cases was significantly higher than the odds of MDD co-occurring in GAD cases (OR=1.52; 95% C.I.=1.05–2.2). Similarly, 12.6% (398/3155) fulfilled the criteria for subthreshold GAD, while 6.1% (194/3155) fulfilled the criteria for subthreshold MDD. Of the subthreshold GAD and subthreshold MDD cases, 58 had subthreshold GAD/MDD comorbidity. Hence, the prevalence of subthreshold comorbidity

Table 2. Differences in functional health for grades of anxiety/depression, and no anxiety/depression.

Diagnostic group	N	Subject feels currently ill: % yes	Subject feels disability from symptoms: % extremely	Feels better off dead % everyday	Somatic complaints % yes	Receiving formal psychological help: % Yes	Pain feeling % extreme amount	Negative feeling % always
Only MDD*	78	49.4	21.3	28.2	36.4	4.0	6.5	25.6
Only GAD*	153	46.4	12.4	7.9	37.5	6.0	5.9	14.5
Comorbid MDD/ GAD*	84	71.4	36.9	35.7	51.2	14.6	16.7	46.4
MDD comorbid subthreshold GAD	48	68.8	20.8	23.4	54.2	10.6	6.3	25.0
GAD comorbid subthreshold MDD	36	52.8	25.0	8.3	38.9	2.9	8.3	25.0
Comorbid subthreshold MDD/GAD	58	50.0	17.2	6.9	43.1	10.7	3.4	15.5
Only subthreshold GAD	292	48.5	9.2	3.8	38.5	7.6	3.1	4.1
Only subthreshold MDD	100	37.0	13.1	11.1	28.0	5.0	13.0	13.1
No GAD/ MDD	2306	32.3	2.9	2.4	27.4	3.1	3.6	2.8
All subjects	3155	37.2	6.5	5.1	30.6	4.3	4.5	6.4
Statistics for all subjects		$\chi^2=120.2$ $Df=8$ $P<0.0001$	$\chi^2=861$ $Df=40$ $P<0.0001$	$\chi^2=487$ $Df=24$ $P<0.0001$	$\chi^2=195$ $Df=40$ $P<0.0001$	$\chi^2=228$ $Df=4$ $P<0.0001$	$\chi^2=215$ $Df=32$ $P<0.0001$	$\chi^2=650$ $Df=32$ $P<0.0001$

* Compared with MDD only and GAD only groups respectively, the MDD/GAD comorbidity had higher tendency, to feel sick ($\chi^2=7.1$; 12.7, $df=1$, $P<0.001$); feel extreme functional disability ($\chi^2=3.9$; 18.1, $P<0.05$, 0.0001); daily feel better off dead ($P>0.05$; $\chi^2=26.8$, $P<0.0001$); have somatic complaints ($P=0.08$; 0.06); seek formal help ($\chi^2=3.9$, 3.7 $P<0.05$); feel extreme pain ($P=0.08$; $\chi^2=6.0$, $P<0.01$); and have negative feelings ($\chi^2=6.7$, $P<0.009$; $\chi^2=27.2$, $P<0.0001$).

among subjects with subthreshold GAD was 14.6% (58/398), while the prevalence of subthreshold comorbidity among subjects with subthreshold MDD was 29.9% (58/194). Thus, the odds of subthreshold GAD co-occurring in subthreshold MDD cases was significantly higher than the odds of subthreshold MDD co-occurring in subthreshold GAD cases (OR=2.2; 95% C.I.=1.5–3.3). In other words, at the threshold and subthreshold levels, there was a significantly greater likelihood of anxiety occurring in depression than of depression occurring in anxiety.

Differences in socio-demographic characteristics (Table 1)

The higher prevalence of women in all categories of anxiety and depression was more than could be accounted for by chance ($\chi^2=25.1$, $df=8$, $p<0.0001$). Threshold comorbid GAD/MDD cases were significantly older than those with MDD ($t=2.7$, $df=160$, $p<0.008$) and GAD ($t=2.1$, $df=235$, $p<0.03$), but not significantly older than the no psychopathology group ($p>0.05$). Furthermore, subjects with GAD and MDD were significantly younger than subjects in all other categories ($F=3.4$, $df=3149$, $p<0.0001$). In addition, there was no significant difference in age between those with any level of comorbidity ($p>0.05$). Subjects with threshold comorbid GAD/MDD were significantly more likely to be divorced than those with GAD and MDD, as well as

those without significant psychopathology ($\chi^2=64.7$, $df=16$, $p<0.0001$). The tendency for a higher prevalence of unemployment among threshold comorbidity cases did not reach significance ($p>0.05$).

Differences in functional health status (Table 2)

The following pattern emerged. First, there was a monotonic increase in the prevalence of subjects with the severest experience of indices of functional health abnormality, such that, for all items, those with no significant psychopathology had the least prevalence, followed by subthreshold cases, while those with comorbid threshold GAD/MDD had the highest prevalence ($\chi^2=120-861$, $p<0.00001$). Second, compared with the MDD only and GAD only groups, respectively, the threshold MDD/GAD comorbidity group had higher tendency to feel sick ($p<0.001$), feel extreme functional disability ($p<0.05$; $p<0.0001$), daily feel better off dead ($p>0.05$; $p<0.0001$), have somatic complaints ($p=0.08$; 0.06), seek formal help ($p<0.05$), feel extreme pain ($p=0.08$; $p<0.01$), and have negative feelings ($p<0.009$; $p<0.0001$) (Table 2). Third, judging by these measures, it appears that GAD represented a less severe condition than MDD, especially for feelings of functional disability and suicidal ideation ($p<0.05$). Fourth, those with MDD (compared with those having single subthreshold conditions) tended to have a higher frequency of subjects with severe experience ($p<0.05$ for disability,

Table 3. Differences in prevalence (%) of severest state of MDD symptoms experienced (everyday) for comorbidity groups.

Diagnostic group	N	Little interest in things %	Feeling depressed %	Sleep %	Tired or little energy %	Poor appetite %	Feel bad about self %	Concentration difficulty %	Move slowly %
Only MDD	78	67.9	73.1	57.9	53.8	57.1	37.7	41.0	43.6
Only GAD	153	6.6	11.8	24.2	17.4	23.2	11.2	11.2	9.2
Comorbid MDD/ GAD	84	72.6	74.7	61.9	66.7	56.0	44.6	53.6	39.3
MDD comorbid subthreshold GAD	48	83.3	54.2	65.2	52.1	48.9	29.2	39.6	33.3
GAD comorbid subthreshold MDD	36	16.7	27.8	35.3	30.6	33.3	25.0	19.4	13.9
Comorbid subthreshold MDD/GAD	58	15.5	12.1	22.8	19.0	29.8	13.8	10.3	10.3
Only subthreshold GAD	292	3.5	4.8	17.4	16.0	16.3	5.2	9.6	6.8
Only subthreshold MDD	100	25.5	14.1	28.1	26.0	27.8	12.5	16.3	21.2
No GAD/ MDD	2306	3.5	2.3	7.7	7.4	8.2	3.2	4.8	3.9
All subjects	3155	16.9	18.9	14.2	13.2	14.1	6.8	9.0	7.6
Statistics		$\chi^2=167$ $Df=24$ $P<0.0001$	$\chi^2=1718$ $Df=24$ $P<0.0001$	$\chi^2=740$ $Df=24$ $P<0.001$	$\chi^2=756$ $Df=24$ $P<0.001$	$\chi^2=572$ $Df=24$ $P<0.0001$	$\chi^2=619$ $Df=24$ $P<0.0001$	$\chi^2=579$ $Df=24$ $P<0.0001$	$\chi^2=599$ $Df=24$ $P<0.0001$

Table 4. Differences in prevalence (%) of severest state of GAD symptoms experienced (> half the days) for comorbidity groups.

Diagnostic group	N	Anxious, worried %	Difficulty controlling worry %	Irritable %	Restless/fidgety %	Muscles tense %
Only MDD	78	50.0	25.0	32.0	42.1	36.4
Only GAD	153	94.8	54.2	65.1	34.9	34.0
Comorbid MDD/ GAD	84	98.8	69.0	76.2	71.4	57.1
MDD comorbid subthreshold GAD	48	39.6	33.3	54.2	41.7	43.8
GAD comorbid subthreshold MDD	36	97.2	50.0	55.6	47.2	45.7
Comorbid subthreshold MDD/GAD	58	27.6	24.1	38.6	40.4	24.1
Only subthreshold GAD	292	22.9	22.0	30.9	23.9	24.1
Only subthreshold MDD	100	28.0	20.6	32.7	37.5	29.6
No GAD/ MDD	2306	13.3	8.3	14.4	10.8	12.1
All subjects	3155	23.4	15.4	22.6	17.9	17.1
Statistics		$\chi^2=1141$ $Df=24$ $P<0.0001$	$\chi^2=825$ $Df=24$ $P<0.0001$	$\chi^2=581$ $Df=24$ $P<0.0001$	$\chi^2=539$ $Df=24$ $P<0.0001$	$\chi^2=406$ $Df=24$ $P<0.0001$



Table 5. Differences in anxiety/ depression scores and QOL domain scores (%) for comorbidity groups.

Diagnostic group	N	Depression mean (SD)*	Anxiety mean (SD) [95% C.I]**	Physical health mean(SD)	Psychol health mean (SD)	Social relations mean (SD)	Environ domain mean (SD)	General facet mean (SD)
Only MDD*	78	19.2 (4.2)	16.9 (3.4)	54.6 (17.5)	49.0 (16.2)	55.6 (25.9)	52.8 (18.1)	62.0 (20.5)
Only GAD*	153	10.5 (4.4)	18.8 (2.6)	59.7 (17.7)	54.6 (17.4)	60.9 (23.2)	58.3 (15.6)	63.1 (21.3)
Comorbid MDD/GAD*	84	20.2 (3.9)	21.0 (2.5)	44.7 (19.6)	37.9 (15.7)	41.3 (23.9)	42.3 (19.2)	50.9 (24.3)
MDD comorbid subthreshold GAD	48	18.6 (4.3)	18.5 (2.3)	51.7 (15.7)	42.9 (14.9)	51.1 (20.9)	48.5 (14.7)	56.5 (17.7)
GAD comorbid subthreshold MDD	36	14.6 (3.7)	18.9 (2.8)	51.4 (19.9)	47.3 (17.1)	53.2 (22.0)	51.7 (15.1)	50.0 (25.2)
Comorbid subthreshold MDD/GAD	58	14.1 (3.2)	17.7 (2.3)	61.2 (16.5)	53.2 (15.9)	60.9 (20.0)	57.9 (16.5)	66.1 (21.5)
Only subthreshold GAD	292	9.4 (4.1)	16.6 (2.4)	60.6 (15.6)	60.6 (14.0)	63.7 (21.4)	61.3 (15.6)	63.7 (20.8)
Only subthreshold MDD	100	14.2 (3.2)	16.4 (3.3)	58.1 (17.9)	58.2 (13.6)	61.4 (20.1)	62.5 (15.6)	65.3 (22.1)
No GAD/MDD	2306	5.9 (4.7)	12.8 (3.4)	70.0 (17.1)	66.7 (16.7)	70.6 (20.6)	66.4 (17.7)	73.8 (20.4)
All subjects	3155	7.9 (5.9)	14.1 (3.9)	66.6 (18.2)	63.2 (17.7)	67.3 (21.9)	63.8 (18.1)	70.5 (21.5)
Statistics for all subjects		$F=270.6$ $P<0.001$	$F=198$ $P=0.001$	$F=51.9$ $P<0.0001$	$F=66.6$ $P<0.0001$	$F=33.7$ $P<0.0001$	$F=36.3$ $P<0.0001$	$F=32.9$ $P<0.0001$

* Maximum score =27; ** maximum score =24; Df: 8/3133. Subjects with comorbid MDD/GAD had significantly higher depression and anxiety scores than other categories; and lower QOL than other categories ($P<0.001$).

somatic complaints and negative feelings). Fifth, the co-occurrence of subthreshold conditions tended to lead to an increase in the prevalence of subjects with more intense experience of symptoms. This was more so for GAD than for MDD because subjects with comorbid threshold GAD/subthreshold MDD had significantly higher prevalence of experience of severe functional symptoms for most items in comparison with subjects in the GAD only category ($p<0.05$).

Differences in symptom profiles and anxiety/depression scores between groups (Tables 3 and 4)

The above pattern of quantitative differences was also evident for the symptoms of anxiety and depression. First, using the example of depression (Table 3), there was a monotonic increase in the prevalence of subjects with severest experience of symptoms ("everyday"), starting from those without significant symptoms through subjects with subthreshold anxiety, only GAD, subthreshold depression, and MDD, to threshold GAD/MDD comorbidity ($\chi^2=167-1718$, $p<0.0001$). Second, those with MADD had mostly similar prevalence of severe experience compared with subthreshold MDD. The tendency for threshold GAD/MDD comorbidity cases to have higher prevalence of severe experience compared with MDD only cases was not significant ($p>0.05$).

Similarly for anxiety, there was a monotonic increase in the prevalence of subjects with the severest experience of symptoms ($\chi^2=406-1141$, $p<0.0001$). However, unlike in the case of depression, subjects with threshold GAD/MDD comorbidity had significantly higher prevalence of those with severest

experience for most symptoms of anxiety compared with GAD only cases ($p<0.05$). In addition, subjects having GAD with comorbid subthreshold depression had similar prevalence of severe symptom experience in comparison with GAD only cases. Also, those with MADD had similar prevalence of severe symptom experience compared with subjects with only subthreshold anxiety and subthreshold depression.

Differences in profile of anxiety and depression scores (Table 5).

In line with the above pattern, there was a monotonic increase in anxiety and depression scores, starting from those with no significant symptoms, through the subthreshold conditions, to the group with threshold GAD/MDD comorbidity having the highest scores ($p>0.0001$). While the tendency for the threshold GAD/MDD comorbidity group to have higher depression scores than the MDD group did not reach significance ($p>0.05$); the trend was significant for all other groups, including the GAD ($t=16.9$, $df=235$, $p<0.0001$), and MDD comorbid subthreshold GAD ($t=2.2$, $df=130$, $p<0.03$). Also, the threshold GAD/MDD comorbidity group had significantly higher anxiety score than all the other groups ($t=6.3$, $p<0.0001$).

Differences in QOL domain scores between groups (Table 5)

In all domains there was a monotonic decrease in QOL with increasing anxiety/depression symptoms and anxiety/depression comorbidity. Hence, the group without significant

psychopathology had the highest scores, followed by the sub-threshold condition groups, with the threshold GAD/MDD comorbidity group having the lowest scores ($F=32.9-66.6$, df 8/3133, $p<0.0001$). In all domains the scores for subjects with comorbid MDD/GAD were less than 1SD of the scores for subjects without depression/anxiety. For example, the domain scores of the no psychopathology group at the threshold of 1SD were 52.9; 48.4; 50.0; 48.7; 53.4, respectively, for physical health, psychological health, social relations, environment domain and general facet. When compared with the mean scores for subjects with comorbid MDD/GAD, the scores were consistently less than 1SD of the scores for subjects without significant anxiety/depression. This is in support of the recommendation by Varni et al. [85], that a QOL domain score of <1SD population mean should indicate subjects at risk for poor QOL [81].

In line with the impression from the functional health indices that GAD represents a less severe clinical condition than MDD, subjects with GAD had higher QOL domain scores than subjects with MDD. This trend reached significance for the following domains: physical health ($t=2.1$, $df=229$, $p<0.04$), psychological health ($t=2.4$, $p<0.02$) and environmental domain ($t=2.4$, $p<0.02$). In addition, the presence of subthreshold conditions tended to further diminish the QOL of those with GAD and MDD (ie, group with GAD > comorbid GAD/ subthreshold depression; while MDD > comorbid MDD/ subthreshold GAD). This trend reached significance for the following domains: (i) physical health: GAD group ($t=2.5$, $df=187$, $p<0.01$); (ii) psychological health: MDD group ($t=2.1$, $df=124$, $p<0.04$); GAD group ($t=2.3$, $p<0.02$); (iii) environment domain: GAD ($t=2.3$, $p<0.02$); and (iv) general facet: GAD ($t=3.2$, $p<0.002$). As a proxy for severity, subjects with MADD had QOL domain scores that were mostly similar to those of subjects with GAD.

Multivariate analyses

The impact of age, anxiety and depression scores on group differences in QOL

In view of the impact of anxiety, depression and age on QOL as shown above, we re-analyzed the data on group differences in QOL by ANCOVA, with age and the scores on anxiety and depression as covariates. However, after adjusting for age, the group differences in QOL, previously noted, still remained. For anxiety and depression scores, however, the following pattern emerged after adjusting for anxiety and depression scores: (a) Physical health – the previously noted significant group differences in the physical health domain were no longer significant ($p>0.05$); (b) Psychological health – most of the group differences were no longer significant, except that the no psychopathology group had significantly higher score than the threshold GAD/MDD comorbidity group, at a diminished level of significance ($p<0.02$); (c) Social relations – most of the group differences were no longer significant, except that the no psychopathology group, the MDD group, the MADD group, and the subthreshold MDD group all had significantly higher scores than the threshold MDD/GAD comorbidity group (p mostly <0.05); (d) Environment domain – most of the group differences were no longer significant, except that the no psychopathology group and subthreshold MDD group still had significantly higher QOL than the

threshold GAD/MDD comorbidity group ($p<0.001$); and (e) General facet – group differences were no longer significant. We conclude from the ANCOVA results that, whereas the group differences in QOL scores were mostly mediated by the severity of symptoms of anxiety and depression, this result was most characteristic of the other comparison groups (ie, MDD, DAD, subthreshold conditions, and no psychopathology). The threshold GAD/MDD comorbidity group still differed from the no psychopathology group from the perspective of psychological health, social relations and environment domain.

Comparison of profile of predictors of QOL

We found the following pattern, using the independent variables that entered the final regression equation: (i) for the MDD group, the only significant predictor of QOL was the anxiety score (12.6% of variance, Beta = -0.36, $p<0.004$); (ii) for the GAD group, the significant predictors were gender (5.5% variance), occupation (6.3%), marital status (6.9%), suicidal ideation (4.4%), and anxiety score (3.9%); (iii) for the threshold GAD/MDD comorbidity group, the significant predictors were age (10.1% of variance) and feeling ill (7.3%); (iv) for the comorbid subthreshold anxiety – depression group, the predictors were marital status (17.8%) and feeling ill (7.5%); and (v) for the no psychopathology group, there were 7 significant predictors: age (1.2%), education (0.4%), functional disability (10.7%), suicidal ideation (3.8%), feeling ill (2.2%) and depression (0.9%). In other words, while the predictors of subjective well-being for the no psychopathology group were similar to what is known for well groups in the general population [83], the psychopathology groups were characterized by different sets of predictors in this regard.

DISCUSSION

Overview

In pursuit of the research question on whether there is differentiating meaningfulness between comorbid threshold GAD/MDD on the one hand, and the corresponding “pure” single disorders, on the other hand [17,18], we assessed the characteristics of subjects with sufficient symptoms of these conditions in an Arab general population sample. We used outcome measures that had the potential to demonstrate qualitative and quantitative differences. The relatively high prevalence of threshold comorbidity (30.8–40%) is in line with the literature [7,22], indicating the universality of this finding [32]. The odds of anxiety co-occurring in depression were significantly higher than the odds of depression co-occurring in anxiety at the threshold and subthreshold levels [5].

Based on the quantitative measures, our findings are in line with a dimensional model in which subthreshold conditions are at the lower end of a continuum, followed by GAD and MDD, with comorbid threshold MDD/GAD at the upper end [2]. Based on the qualitative measures, the disorders seemed to be distinguished by age and predictors of subjective QOL. Within the limitations of the study, therefore, our results give some support to Tyrer’s idea of comorbid threshold anxiety-depression as “cothymia” [32], which is validated by recent theoretical models of psychopathology

[3]. However, the difficulty of obtaining precise results in this type of inquiry is a reflection of the observation that, in the existing categorical systems of diagnosis, we are dealing with a flawed system where there are no clear boundaries between classes [86].

Differences in socio-demographics

Our finding that subjects with sufficient symptoms of comorbid threshold GAD/MDD were significantly older and more likely to be women, divorced and unemployed, compared with GAD and MDD cases, has much support in the literature. In the National Comorbidity Study Replication [8], it was found that while anxiety had earlier age of onset than depression, those with comorbid conditions had later onset. Another USA study of children/adolescents found that those with comorbid anxiety-depression were older and had more severe conditions [16]. In a Dutch general population study, those with comorbid anxiety-depression were more likely to be women, not married, less educated, and younger [1]. In a UK general population study, those with comorbidity were older, less likely to be married and of lower education [2]. In view of the majority finding of older age for the comorbidity group, it is reasonable to suggest that the comorbidity cases may simply be subjects with the "pure" disorders who progressed to the more severe condition – represented by comorbidity. However, this idea is not supported by the results of a 32-year follow-up study from New Zealand [5]. Furthermore, in cases of mental disorders comorbid with physical illnesses, it was found that the prevalence of this comorbidity increased with age [10]. Hence, more data is needed to determine whether the age differences reflect one way in which comorbid anxiety-depression differs qualitatively from the "pure" disorders. However, the poorer social circumstance (eg, marital and occupational status) of those with comorbidity may reflect the impact of a more severe clinical condition on social functioning.

Functional and clinical severity

In all the measures of severity, the comorbid threshold GAD/MDD cases were at the highest end of a dimension of continuum. This is the most robust finding in the literature [4,6,7,33]. However, it would be erroneous to consider comorbidity to be a separate disorder simply because of quantitative differences [87]. Hence, coupled with popular doubts about the categorical nature of psychopathology, we prefer to interpret our results as being in line with the suggestion that the boundaries between disorders in the same psychopathology class exist in a dimension that consists of levels of severity, while different classes exist in hierarchies [39,86,88,89]. Krueger and Markon [3] have made illustrations of such a model. This is in line with the hierarchy of classes of illness proposed by Foulds and Bedford [90], in which the more severe a mental condition is, the more likely it is to include the symptoms of conditions beneath it in the hierarchy of conditions. This explains our finding that MDD, as a more severe condition, was more likely to have co-occurring GAD, in comparison with GAD, which was relatively less likely to have co-occurring MDD, at the threshold and subthreshold levels. Furthermore, in an examination of the role of latent variables in the development of comorbidity among 18 mental disorders, it was

found that common causal pathways (internalizing and externalizing factors) accounted for most of the comorbidity, and the presence of one disorder predicted the subsequent onset of other disorders, especially within the same (internalizing or externalizing) domain [7]. In other words, it is quite possible for anxiety and depression to be distinct abnormal experiences, yet for the symptoms and disability that they cause to be described as existing along a dimension of severity [89].

In view of the fact that we did not interview the subjects, it could be argued that some of our GAD cases may have occurred in the course of mood disorders, which is a major exclusionary criterion for diagnosing GAD in the DSM-IV. However, it has been shown that GAD occurring within the course of MDD has a level of severity that is similar to MDD [91]. Hence, our finding that GAD represented a less severe condition than MDD [5] is an indication that our GAD cases were probably not disorders occurring within the course of mood disorders [91].

Predictors of QOL

As expected, there was a monotonic decrease in all domains of QOL, so that those with comorbid threshold GAD/MDD had the lowest scores [83,92,93]. First, our findings validate the recommendation that subjects at risk status for poor QOL should be judged by those with $<1SD$ of the score for the normal population [81,85]. Second, it could be argued that one indication of qualitative difference is that, after adjusting for scores on anxiety and depression, it was only the comorbid threshold GAD/MDD group that still had significant differences in some QOL domains, compared with the no psychopathology group. In other words, while the differences in QOL between the no psychopathology group and the GAD and MDD groups could be mostly accounted for by the dimension of severity of depression and anxiety [81,92,93], the QOL of the comorbidity group differed in more ways. Third, we suggest that, within the limitations of this measure, our most obvious evidence of differential meaningfulness is the finding of distinct differences in the pattern of predictors of subjective well-being for the groups. Whereas the no psychopathology group had predictors of QOL that were in line with what is known about the general population [51,83,94], the psychopathology groups differed, with the GAD and MDD groups being more similar to each other and markedly different from the comorbid threshold GAD/MDD group.

Limitations

The major limitations of the study are the cross-sectional design, the subjects were not interviewed, and the non-inclusion of data on family history and age at onset, which could have helped to assess group qualitative differences [43,87]. To make up for not interviewing the participants in sorting the cases into categories, we followed a method that has been used by others [24], and we minimized the issues of reliability and validity by the fact that we strictly followed an algorithm based on DSM-IV criteria and jointly agreed on all cases.

While our use of a general population sample and focus on symptom-level data are advantageous, as previously noted

[11,18,35,48], our findings have limited application to the condition of clinical samples. Although we could not fulfill the DSM-IV requirement to exclude the possible contribution of physical illnesses, bereavement and mood disorders to the symptoms, the validity of these exclusionary clauses for GAD and MDD has been challenged [20,27,91]. Furthermore, the DSM-IV exclusionary clause for the presence of mood disorders in diagnosing GAD may not apply to our sample because GAD was a less severe condition than MDD [91]. The other limitations are inherent in the categorical system of classification [14,86], the observation that the definition of subthreshold conditions can lead to a high potential for false positives [20,28], and that the diagnosis of DSM-IV GAD is less reliable because some of the defining symptoms lack specificity [14]. We tried to overcome these limitations by our rather more stringent symptom requirements for sorting the subjects into categories, and by making our operational definitions to correspond with the DSM-IV. Although it is arguable whether our use of the predictors of QOL as a qualitative measure of difference between groups is valid, this methodology is supported by the current search for the genetic underpinnings of symptoms of patient-reported outcomes and QOL [78–80].

CONCLUSIONS

The relatively high rate of comorbidity among those with GAD and MDD supports the recommendation to assess these disorders routinely, regardless of the primary reason for consultation [47]. This includes attention to subthreshold conditions [29,95]. However, our data did not support MADD as being meaningfully different from the single subthreshold conditions. Furthermore, the demonstrated high prevalence of comorbidity calls for specific treatment trials on comorbid GAD/MDD, because there are no adequate treatments for this condition [26], and there are doubts about the effectiveness of SSRIs/SNRIs [96].

From the perspective of a dimensional model, our findings support the notion of comorbid threshold GAD/MDD as being at the higher end of a continuum of symptoms [2,41], probably with a later onset, and differing from the “pure” conditions by the pattern of predictors of subjective well-being. To support this notion, borrowing from a discussion on the psychoses [97], the commonality in the efficacy of SSRIs/SNRIs for GAD and MDD [26,34] points to the possibility that these disorders and their comorbidity are dimensional.

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