Difficult birth, difficult life?

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CHAPTER 7

QUANTIFYING PSYCHIATRIC COMORBIDITY LESSONS FROM CHRONIC DISEASE EPIDEMIOLOGY

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Abstract

Background

Comorbidity research in psychiatric epidemiology mostly uses measures of association like odds or risk ratios to express how strongly disorders are linked. In contrast, chronic disease epidemiologists increasingly use measures of clustering, like multimorbidity (cluster) coefficients, to study comorbidity. This article compares measures of association and clustering.

Methods

Narrative review, algebraical examples, a secondary analysis of an existing dataset and a pooled analysis of published data.

Results

Odds and risk ratios, but the former more than the latter, confound clustering with coincidental comorbidity. Multimorbidity coefficients provide a pure estimate of clustering which is the proportion of the association between disorders that is of etiological interest. Odds and risk ratios can express comorbidity between no more than two disorders, whilst clustering coefficients, although computationally laboursome, can capture multimorbidity of any number of disorders. Cluster coefficients depend less on the prevalence of illness in study groups than measures of association.

Conclusion

Odds and risk ratios are well suited for comorbidity research which focuses on which sets of disorders or syndromes tend to occur in combination and the implications of this for, for instance, nosological classification, a traditional interest of psychiatric epidemiology. However, the cluster coefficient is to be preferred if the interest is more aetiological, addressing for example why certain individuals are prone to multiple health problems.

Introduction

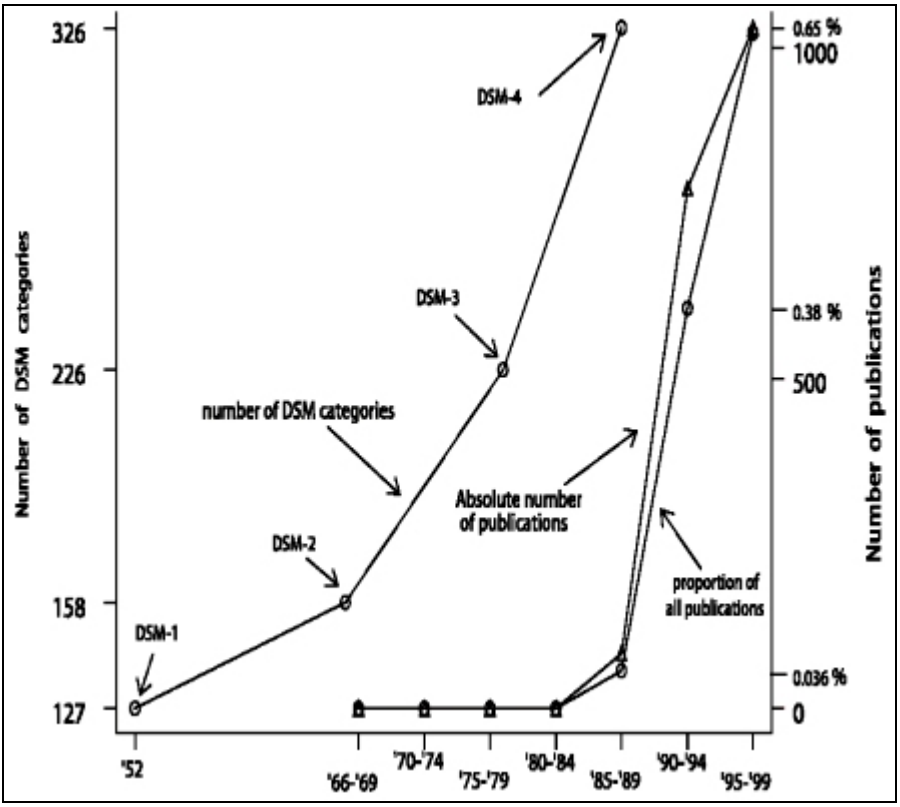
The term comorbidity was introduced in 1970 by Feinstein.[1] His interest was the prognosis of chronic somatic disease and he defined comorbidity as the occurrence of other medical conditions additional to an index disease.[1] From the mid-1980s onward comorbid occurrence of disorders also, and increasingly, aroused the interest of psychiatrists. The first psychiatric publication on comorbidity appeared in 1985[2], 15 years after Feinstein introduced the term. Psychiatrists' interest in the phenomenon was probably sparked off by the publication, in 1980, of the third edition of the Diagnostic and Statistic Manual of Mental Disorders. This expanded the number of psychiatric diagnoses from 158 in the previous edition to 226, thus also increasing the potential for overlap between disorders.[3] The trend toward ever more fine-grained classification has not halted yet and, in its wake, the explosion of psychiatric research papers on comorbidity continues (Fig. 7.1).

The classification of psychiatric morbidity is less fixed than that of somatic disorders. When diagnostic categories are found to be strongly associated, diagnostic systems may come in for revision as a result. Indeed, the strength of associations between sets of diagnoses is the subject of most publications on psychiatric comorbidity and the implications of comorbidity for disease classification have occupied psychiatric epidemiologists more than its effects on prognosis.[5] In this search for associations, the fact that a substantial part of the epidemiological overlap between disorders is statistically inevitable is easily overlooked. This paper examines the dependence of comorbidity on background rates of morbidity in populations and the implications of this for its quantification.

Definition and classification

Joint occurrence of disorders has been defined in a number of ways, according to the number of conditions considered, their degree of overlap in time, and the mechanisms responsible.

Fig. 7.1 Classificatory progress (DSM) and absolute and proportionate number of publications (PsycLit) featuring "comorbid" in title or abstract



Comorbidity versus multimorbidity

As indicated, the term comorbidity was originally used to indicate that a certain index disorder is accompanied by one or more other conditions.[1] This definition implies that the main interest is on the index condition and the effects other conditions may have, for instance on its prognosis. More recently, the term multimorbidity has been introduced in chronic disease epidemiology to refer to any co-occurrence of two but often more than two medical conditions within a person.[5] The introduction of this term indicates a shift of interest from a given index condition to the individuals who suffer multiple disorders. It is gaining wide acceptance in the somatic literature but has appeared no more than ten times in psychiatric research publications to date. Still, many aspects of psychiatric research on comorbidity actually concern multimorbidity: over 14% of respondents in the US National Comorbidity Survey had a lifetime history of three or more different psychiatric disorders.[6]

Episode versus lifetime comorbidity

Feinstein's original comorbidity concept[1] referred to what is now known as episode comorbidity (the occurrence of more than one disorder within the same person in a specific time span[7]). The time span mostly refers to a period of 1–12 months. It has been contrasted with lifetime comorbidity (the occurrence of more than one disorder in a person's whole life[7]) but it should be noted that the distinction between the two is relative since, when episodes are prolonged, they may eventually cover entire biographies. Psychiatric episode comorbidity is reported on more frequently than lifetime comorbidity. This may be because valid lifetime data are harder to come by, but also because, for those who have the refinement of diagnostic classifications in mind,more information can be gleaned from disorders which overlap in time than from the life-history of individuals who suffered multiple disorders over time but never simultaneously. As in the distinction between comorbidity and multimorbidity, the focus on co-occurrence

of disorders in short periods rather than in persons indicates that psychiatry's interest in comorbidity has been primarily disorder- (or: diagnosis-) driven.

Responsible mechanisms

Disorders may co-occur through bias, coincidence or because substantive associations exist between them.

Bias

The best-known example of this is Berkson's bias, referring to the concentration of comorbid cases among hospital- treated patients.[8] Overreporting or increased self-scrutiny may lead to inflated estimates of comorbidity associated with certain conditions like depression.[9] A special type of classification bias arises when diagnostic boundaries are imposed where none exist.[4]

Coincidental comorbidity

Even when disorders are completely independent of one another, in any study population, they can be expected to co-occur at a rate which equals the product of the prevalences of the separate conditions.[9] Thus, comorbidity rates will be higher in "sicker" populations. This proportion of comorbidity which is to be expected statistically, has been referred to as coincidental[5] or independent.[10] We will use the former term.

Substantive associations

When comorbidity rates exceed those which are statistically expected (coincidental) and bias has been excluded, there must be substantive associations between the disorders involved. This proportion of comorbidity has been referred to as cluster[11] (the term we will use), dependent[10] or associative.[5] A lot has been written about how and why disorders may occur in combination more often than expected[12] but, essentially, either of two processes, alone or in combination, must operate; the disorders involved share risk factors or the disorders act, directly or indirectly, as risk factors for one another.

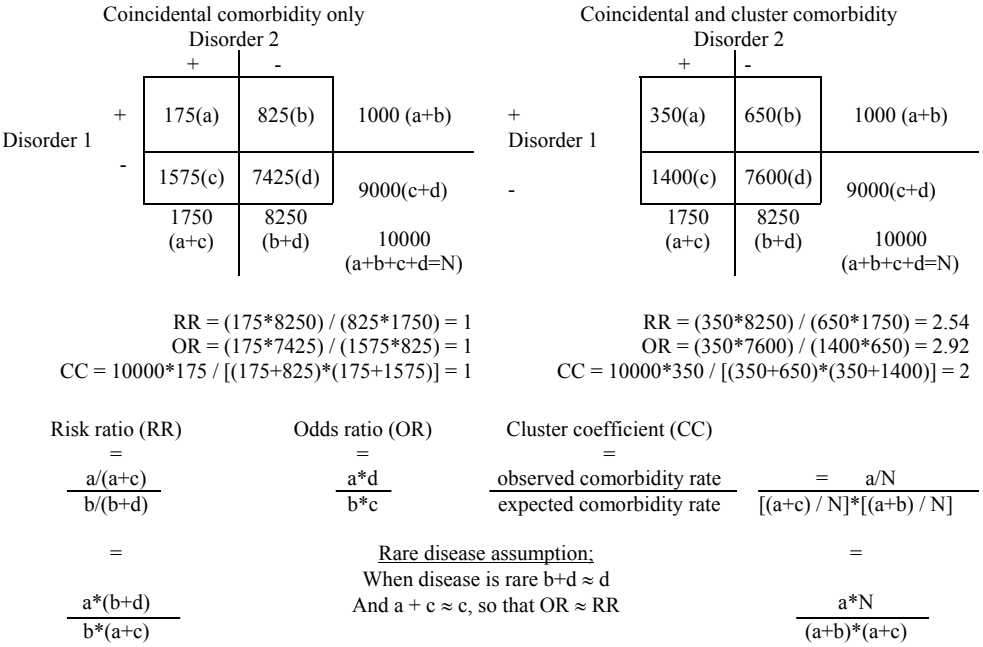
Quantifying cluster comorbidity and multimorbidity

The risk or rate ratio is the preferred measure of association in psychiatric epidemiology and odds ratios are used as an approximation in case control designs. The popularity of the odds ratio is principally due to the ease of its calculation (being simply the cross-product from a two-by-two table) and to the fact that it provides a good estimate of the relative risk, although when disorders are more prevalent its value becomes progressively larger than that of the risk ratio[13] (Fig. 7.2). All major reports on psychiatric comorbidity, like those arising from the National Comorbidity Survey[6], the OPCS Survey of Psychiatric Morbidity[14], the Dutch NEMESIS study[15] and others, quantify comorbidity with odds ratios. However, odds and risk ratios merely express how strongly two diagnoses or disorders are associated and are ill suited for the study of cluster comorbidity and of multimorbidity.

Separating coincidental from cluster comorbidity

Odds and risk ratios estimate the overall strength of association between disorders but fail to separate cluster from coincidental comorbidity. The numerical example in Fig. 7.2 of a cohort of 10,000 persons of whom 10% have disorder A and 17.5% disorder B, illustrates this. When comorbidity is merely coincidental, odds/risk ratios as well as cluster coefficients are all equal to one, indicating that the disorders are not associated and do not cluster. However, when clustering does occur, the value of the cluster coefficient, which divides the observed rate of comorbidity by the rate which is expected under the nullhypothesis of no substantive associations between the separate disorders, is smaller than the values of odds and risk ratios.

Fig. 7.2 Risk ratios, odds ratios and cluster coefficients; divergence in case of higher than coincidental comorbidity (two disorders with prevalences of 10 % and 17.5 %)



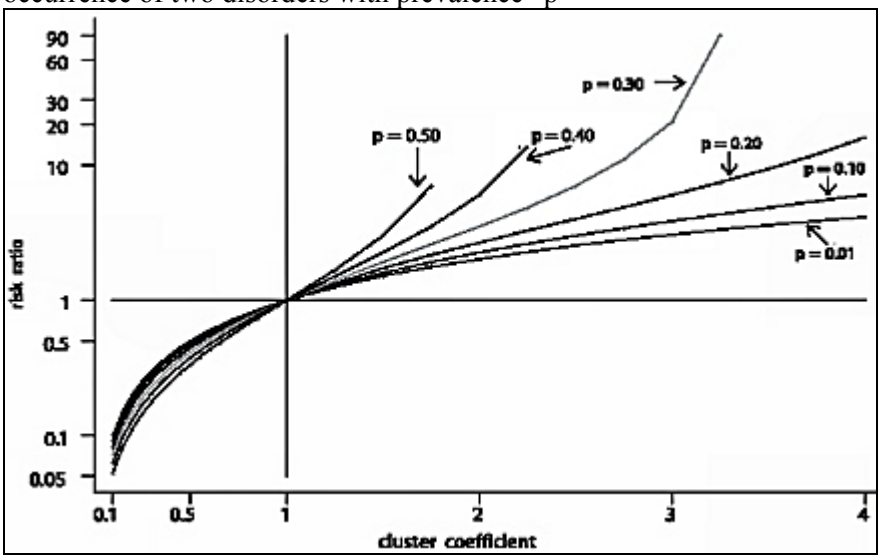
This disjunction arises because the latter two statistics do not adjust overall associations for coincidental comorbidity. Fig. 7.3 illustrates this phenomenon indicating that odds and risk ratios (and the former more than the latter,due to violation of the rare disease assumption[13]), are always, except in the situation of no association, farther away from unity than multimorbidity coefficients and increasingly so as clustering (or its reverse: antagonism) between disorders grows more pronounced. A similar phenomenon arises when the prevalence of the separate disorders in the study population rises. Fig. 7.4 plots risk ratios against

cluster coefficients at varying rates of the separate conditions (for simplicity's sake the separate conditions are assumed to occur at equal prevalences). It illustrates that the cluster coefficient is always nearer to unity (no substantive link) than the risk ratio [and, thus, also the odds ratio which deviates more from unity than the risk ratio (Fig. 7.3)].

The fact that measures of association diverge increasingly from cluster coefficients when clustering increases and when the prevalence of morbidity rises indicates that their use is least appropriate in "sicker" populations.

Fig. 7.3 Relation between cluster coefficients, odds ratios and risk ratios for comorbidity between two disorders with prevalences of 10 % and 17.5 % respectively

Fig. 7.4 Relation between risk ration and cluster coefficient for the joint occurrence of two disorders with prevalence "p"



Combinations of multiple disorders

Joint occurrence, in persons or episodes, of more than two psychiatric disorders is no exception[6] but odds and risk ratios can manage associations between two categorical outcomes only. By contrast, the cluster coefficient can be calculated for any number of disorders, merely by dividing observed and expected numbers of cases. In this case it is sometimes referred to as the multimorbidity coefficient. Calculation of the expected rates is computationally laboursome given the large number of combinations to be considered when more disorders than just two or three are studied. For instance, to calculate the rate at which, in a study of eight diagnoses each with different prevalences, any three of these diagnoses can be expected to co-occur, 56 separate probabilities have to be added.[16]*

When n disorders are considered with individually different prevalences p1, p2 . . . pn and one wishes to know the rate at which k of these can be expected to occur together,one calculates the expected rate of [(n!/k!(n-k)!] different combinations. The expected probability of each individual combination is given by the product of the probabilities (p) of the k disorders which do occur multiplied by the product of the probabilities of non-occurrence (1-p) of the disorders which are absent.

Table 7.1 illustrates how the cluster coefficient can summarize evidence of multimorbidity using data on month prevalences of six neurotic disorders and year prevalences of psychotic disorders and alcohol/substance dependence in 9,830 adult (16–65 years) participants of the UK OPCS psychiatric morbidity survey[17].

Table 7.1 Multimorbidity in the OPCS psychiatric morbidity survey[17].
Distribution of 2,653 psychiatric disorders (eight types) over a general population sample (16–65 years)

One-month prevalences: **Any phobia 2%, Depression 2.7%, OCD 1.8%, Generalized anxiety 4.9%, Mixed anxiety-depression 8.2%, Panic disorder 1%** **Year prevalences:** **Schizophrenia 0.5%, Substance and/or alcohol dependence 5.9%**			
Multimorbidity	**Observed**	**Expected**	**Multimorbidity coefficients[a] (95% confidence interval)**
0 disorders	7837	7448.7	1.04 (1.02 – 1.06)
1 disorders	1681	2124.0	0.79 (0.75 – 0.83)
2 disorders	299	148.7	2.01 (1.79 – 2.25)
3 disorders	84	3.55	23.63 (18.85 – 29.26)
4 disorders	23	0.04	532.25 (337.48 – 798.62)
5 disorders	6	0.0004	16306.68 (5984.33 – 35489.66)

[a]All multimorbidity coefficients are significantly different from 1 ($p < 0.050$)

Multimorbidity occurs more frequently than expected and this obtains in particular for combinations of more disorders than two or three only. On the other hand, fewer persons than expected have one diagnosis only. This pattern applies in other surveys as well and is independent of which type of disorder is considered[9]. It suggests that, in cases of multimorbidity, the interest should focus on which types of individuals are prone to multimorbidity rather than on the exact disorders or diagnoses involved.

The context-dependence of cluster comorbidity

It has been demonstrated that overall associations between disorders, as measured by odds and risk ratios, increase in strength in "sicker" populations. The multimorbidity coefficient corrects for this phenomenon in as far as it is attributable to coincidental (expected) cooccurrence of disorders. However, even cluster comorbidity may vary between study populations for reasons other than merely distributional ones. Effects of disorders on one another may be modified by social context. For instance, links between cocaine or alcohol misuse and affective disorder are weaker in periods or places where such substance use indicates less deviance, i.e. is more normative.[18,20] This context-dependence of cluster comorbidity will be demonstrated using published data on the link between alcohol dependence and depression.

Alcohol dependence and affective disorder –context-dependence of the link

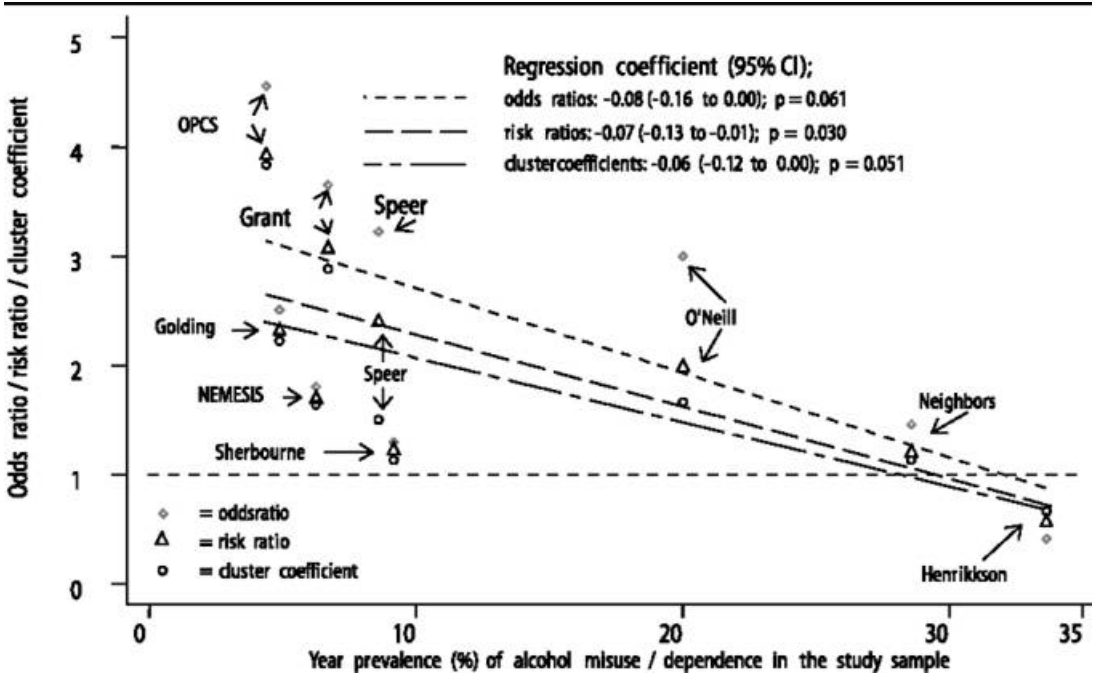
Relevant literature was collected by performing a computer- based search of literature (EMBASE 1989–February 2000; MEDLINE 1987–April 2000; and PSYCHLIT 1987–March 2000) published, with the descriptors alcohol, depression, substance use and/or psychiatric comorbidity in their title. As a second step, all references given in the selected publications were screened. Studies, in any language, which reported numerical data allowing calculation of odds/risk ratios and cluster coefficients were included. For each of these, information is needed on the prevalence of the separate conditions and either the rate of the comorbid condition or at least one measure of association or clustering. Further, only studies with diagnoses based on DSMIIIr (APA 1987) or DSMIV (APA 1994) were included, because DSMIIIr modified criteria for alcohol dependence and misuse. Only comorbidity over a period of 12 months was analysed. Twenty-eight studies appeared suitable at first glance but nine articles eventually remained (Table 7.2).

Table 7.2 Comorbidity and clustering between alcohol dependence and major depression

Study	Sample characteristics	Odds ratio (95% CI)	Risk ratio (95% CI)	Cluster coefficient (95% CI)
LA ECA study[28]	N = 2393 Population sample 18 years and older	2.51 (1.27 - 4.93)	2.33 (1.09 – 4.44)	2.22 (1.07 – 4.10)
Nemesis[15]	N = 7076 Population sample 18 – 65 years	1.80 (1.32 – 2.46)	1.71 (1.25 – 2.30)	1.63 (1.21 – 2.16)
OPCS Survey of Psychiatric Morbidity[17]	N = 10108 Population sample 16 – 64 years	4.56 (2.65 – 7.83)	3.94 (2.23 – 6.47)	3.84 (2.19 – 6.23)
Speer and Bates[29]	N = 128 Psychiatric patients 54 years and older	3.22 (1.40 – 7.40)	2.41 (1.10 – 5.58)	1.50 (0.94 – 2.38)
Neighbors et al.[30]	N = 112 Juvenile delinquents 12 – 28 years	1.46 (0.67 – 3.18)	1.22 (0.66 – 2.19)	1.13 (0.69 – 1.75)
Henriksson et al.[31]	N = 229 Suicide victims 10 – 89 years	0.41 (0.27 – 0.75)	0.58 (0.33 – 0.96)	0.67 (0.39 – 1.00)
Sherbourne et al.[32]	N = 2296 Psychiatric and medical patients 18 years and older	1.29 (1.03 – 1.62)	1.24 (1.01 – 1.52)	1.13 (0.97 – 1.32)
O'Neill[33]	N = 20 American aboriginals 29 – 79 years	3.00 (0.39 – 24.1)	2.00 (0.18 – 14.0)	1.67 (0.20 – 6.02)
NLAES[34]	N = 42862 Population sample 18 years and older	3.65 (3.19 – 4.16)	3.08 (2.73 – 3.47)	2.88 (2.56 – 3.22)

As expected, cluster coefficients are nearer to unity than odds ratios in all, with risk ratios taking an intermediate position. However, the strength of the association, whichever statistic is used to express it, varies considerably between studies. A sizeable proportion of this heterogeneity is attributable to between-study variation in the prevalence of the two separate conditions – associations are weaker in sicker populations but this effect is weakest for the cluster coefficient (Fig. 7.5).

Fig.7. 5 Overall and cluster comorbidity of alcohol misuse/dependence and depression; association with prevalence of alcohol misuse/dependence in study samples



Discussion

It is well known that, like somatic disorders, mental disorders are not distributed at random across populations but cluster in a minority.[9] Several mechanisms may contribute to this. First and foremost, in psychiatry more than in somatic medicine, different clinical manifestations of one disorder may, mistakenly, have been classified as if they were separate disorders.[4,21] Thus, it is debatable whether major depression and generalized anxiety disorder are two different entities or clinical variations of one underlying condition.[22] Secondly, psychiatric disorders may act as risk factors for one another and this may partly explain why substance use co-occurs so often with anxiety and affective disorders.[23] Thirdly, in chronic disease medicine symptom diversity (i.e. comorbidity or (better) multimorbidity) is increasingly seen as an indicator of severity of illness alongside symptom chronicity and intensity. Thus, comorbidity indices have been developed which weigh overall severity of illness according to the number of individual conditions and their seriousness.[24] The cluster or multimorbidity coefficient discussed in this paper is an example of this approach. It is efficient in identifying the extent to which illness concentrates in a sick minority, but, as a pay-off, less effective in identifying which combinations of disorders tend to co-occur most often, a particular interest of nosologists.

If the focus of interest is on the etiology of comorbidity rather than its nosological implications, it is important that a clear separation be made between coincidental and cluster comorbidity. As a statistical necessity, comorbidity rates are higher in populations with higher base rates of illness. The implications of this deserve more attention. For instance, it is unclear whether the relatively high prevalence of psychiatric multimorbidity in young adulthood compared to other ages[6] is in excess of what is to be expected merely on the basis of the fact that the prevalence of psychiatric disorder is in any case at its highest in this group. Adjusting observed comorbidity rates for what can be expected, i.e. calculating the multimorbidity coefficient, would provide the answer.

Adjustment of comorbidity rates for what can be expected will remove some, but not all, of the variation between studies of comorbidity conducted in different settings. However, the heterogeneity that remains is not, like

coincidental comorbidity, a statistical artifact but, rather, representative of a phenomenon of substantive interest. Evidence is accumulating to suggest that the strength of risk-outcome associations in psychiatric epidemiology tends to diminish as exposure to the risk factors in question becomes more widespread.[20] This applies not only to risk factors like ethnic minority status[25] and unemployment[26], but also to problems like cocaine[18] or alcohol misuse[27]. A variety of mechanisms may explain this dilution or concentration of risk[20] by overall morbidity levels. The impact of exposure (for instance, to given levels of alcohol consumption) and, thus, the risk of complications like comorbid depression is less when the exposure is more prevalent (i.e. drinking more normative) – an example of social causation. On the other hand, it requires higher levels of vulnerability (and, thus, high risk of comorbidity) to develop a condition like alcohol dependence in the first place in relatively "dry" groups.[27]

Conclusion

Comorbidity can be studied not only as a feature of disorders but also as a feature of individuals. When the focus is on the latter, measures of clustering – little used in psychiatry – are more appropriate than measures of association as the latter are, of necessity, stronger in groups with more disorders like, in psychiatry, the young. Between-study variation that remains after coincidental comorbidity has been accounted for may indicate important etiological mechanisms operative at the group level.

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