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A simulation study to demonstrate the biases in the diagnoses of mental illnesses: major depressive episodes, dysthymia, and manic episodes

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A simulation study to demonstrate the biases in the diagnoses of mental illnesses: major depressive episodes, dysthymia, and manic episodes

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Keywords: Frailty; bias; forward-stepwise regression; the Health and Retirement Study; index mining

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3	20	Abstract
4	20	
5	21	Objectives
7	21	Composite diagnostia criteria are likely to introduce biases to the diagnoses that
8	22	composite diagnostic citiena are likely to introduce blases to the diagnoses that
9	23	subsequently have poor relationships with input symptoms. This study aims to understand
10	24	the magnitudes of blases introduced to the diagnoses of three mental linesses with large
11	25	disease burdens (major depressive episodes, dystnymic disorder, and manic episodes) and
12	26	the relationships between the diagnoses and the input symptoms.
14	27	Settings
15	27	Settings
16	28	Psychiatric care in general
17	20	Participants
18 19	29	Without we down and data are itable to the mublic 400,000 subjects were simulated and the
20	30	Without real-world data available to the public, 100,000 subjects were simulated and the
21	31	input symptoms were assigned based on the assumed prevalence rates (0.05, 0.1, 0.3, 0.5,
22	32	and 0.7) and correlations between symptoms (0, 0.1, 0.4, 0.7, and 0.9). The input symptoms
23	33	were extracted from the diagnostic criteria of three mental illness. The diagnostic criteria
24	34	were transformed to mathematical equations to convert the input symptoms to diagnoses.
25 26	25	Defense and accordance automatic
27	35	Primary and secondary outcomes
28	36	Biases due to data censoring or categorization introduced to the intermediate variables and
29	37	the three diagnoses were measured. The relationships between the input symptoms and
30 21	38	diagnoses were interpreted using forward stepwise linear regressions.
32	20	Populta
33	39	
34	40	The prevalence rates of the diagnoses were lower than those of the input symptoms and
35	41	proportional to the assumed prevalence rates and the correlations between the input
36 37	42	symptoms. Certain input or bias variables consistently explained the diagnoses better than
38	43	the others. Except for zero assumed correlations and 0.7 prevalence rates of the input
39	44	symptoms for the diagnosis of dysthymic disorder, the input variables could not fully explain
40	45	the diagnoses.
41	4.6	Conclusions
42	46	Conclusions
43 44	47	There are biases introduced to the diagnoses of three mental illnesses, major depressive
45	48	episodes, dysthymic disorder, and manic episodes. The design of the diagnostic criteria
46	49	determines the prevalence of the diagnoses, the relationships between the input symptoms
47	50	and the diagnoses, and the biases introduced. The importance of the input variables has
48	51	been largely distorted by the diagnostic criteria.
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51	52	Irial registration
52	53	Not applicable
53	F 4	Chronoth and limitation
54 55	54	Strength and limitation
55 56	55	1. I he prevalence of three mental illnesses were determined by the prevalence of the
57	56	input symptoms and modified by the diagnostic criteria and correlations between the
58	57	input variables in simulated populations.
59	58	2. Blases due to data censoring or categorization were introduced to the intermediate
60	59	variables and the three diagnoses of mental illnesses in simulated populations.

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- 3. The diagnostic criteria modified the importance of the input variables and certain input or bias variables were given more weights than expected in simulated populations.
 - 4. The design of diagnostic criteria influenced the prevalence. Even with the same input variable prevalence, dysthymic disorder was the most prevalent and major depressive episodes were the lest prevalent in simulated populations.
 - 5. This study is based on simulated data and needs to be verified with real-world data.

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68 Background

The diagnoses of several mental illnesses in patients are made often based on a variety of criteria. These criteria often involve symptoms complained by the patients.[1, 2] For example, the diagnosis of major depressive disorder defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) requires at least one major depressive episodes.[1, 2] For each major depressive episode, the major criteria are "depressive mood and/or loss of interest or pleasure in life activities for at least 2 weeks".[1, 2] In addition to qualify the major criteria, the patients need to report at least five of the nine symptoms that "cause clinically significant impairment in social, work, or other important areas of functioning almost every day", including insomnia or hypersomnia and fatigue or loss of interest. [1, 2] In other words, patients need to match both the major and minor criteria before being diagnosed with a major depressive episode.

Historically this symptom-based diagnostic approach developed by Feighner et al. has been widely accepted. [3, 4] Since then, mental illnesses can be diagnosed through different sets of criteria. This approach is important because clinicians become capable of screening important symptoms before diagnosing and treating patients accordingly. In fact, these criteria can also be seen as composite measures that use multiple measures to capture disorders that may not be quantified with single variables. [5, 6] Recent studies on composite measures have found that composite measures are problematic because biases can be introduced while aggregating information from input variables.[6] The biases emerge while the sums of input variables are censored or while input variables are transformed inadequately.[6, 7] These biases have been proven vital to the diagnosis of frailty syndrome, a condition that often occurs in the elderly and is significant for several health outcomes.[6] For the diagnosis of frailty syndrome using the Biological Syndrome Model,[8] biases alone can explain more than 71% of the variances of the frailty diagnosis.[6]

Designed as composite measures, it is possible that the diagnostic criteria of mental
illnesses also introduce biases to diagnoses so that the diagnoses could not be fully
explained by the input symptoms listed in the criteria. This study aims to first understand the
relationships between mental symptoms and diagnoses and then quantify the potential role
of the biases regarding the diagnoses by simulating populations with different prevalence
rates and between-variable correlations of mental symptoms.

99 Methods

48 100

Assumptions and simulation parameters

101 Simulated populations with mental symptoms of different prevalence rates and 102 between-variable correlations were created to interpret the diagnoses and understand the 103 potential magnitudes of biases that could be introduced via data processing (reproducible 104 using data sets in the S 1 and S 2). Three diagnoses of mental illnesses were chosen for the 105 leading associated disease burdens:[2] major depressive episodes for the diagnosis of major 106 depressive disorder, dysthymic disorder, and manic episodes for the diagnosis of bipolar 107 disorder.[1]

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60108There were assumptions made to simulate the populations (Table 1). First, for each
simulation the prevalence rates of the input symptoms were assumed to be similar for the

three diagnoses evaluated in this study. Second, the input symptoms for the diagnoses of major depressive episodes and dysthymic disorder correlated with the same correlation coefficients and those for the diagnosis of manic episodes correlated to one another.[9] Third, the input symptoms for the diagnosis of manic episodes were created independently of those for the diagnosis of the other two mental illnesses. The assumptions of the prevalence rates and between-variable correlations were made because there was no acceptable-quality data on the symptoms of mental illnesses published. There were studies on the prevalence of mental illnesses, [10, 11] but the information on the prevalence of mental symptoms was very limited. There were variables about depression or anxiety collected in national surveys, such as the items collected through the Center for Epidemiologic Studies Depression Scale.[6, 12-18] However, these variables were not the symptoms used in the DSM-IV-TR. Lastly, we assumed that the diagnoses were made accurately based on the presence of the input symptoms and the diagnostic criteria in the DSM-IV-TR. However, this did not hold in the real world.[19] For simplicity and practical reasons, we assumed perfect diagnostic quality by physicians and accurate reporting of the input symptoms by patients in the simulated populations.

²³²⁴ 126 Diagnostic criteria as mathematical functions

The input symptoms were extracted from the major and minor criteria of the diagnoses and listed in Table 2 to Table 4. The input symptoms, major and minor criteria, and the diagnoses were labelled with new variable names. All input symptoms, items or domains in the major or minor criteria, and the diagnoses were binomial variables, presenting zero and one for the absence and presence of the symptoms, criteria, and the diagnoses respectively. For example, "insomnia" and "hypersomnia" were extracted from one of the minor criteria for the diagnosis of major depressive episodes. "More talkative than usual" and "pressure to keep talking" were extracted from one of the minor criteria for the diagnosis of manic episodes.

Mathematical functions were generated based on the criteria to convert input symptoms into diagnoses. For example, one of the minor criteria of dysthymic disorder was "poor appetite or overeating". This required two input symptoms and one bias variable to generate the criterion.[6] "Poor appetite or overeating" equaling the sum of two input variables, "poor appetite" and "overeating", and a bias variable to achieve censoring of the sum of both variables.[6] The sum of two binomial variables could exceed one and the bias variable had values of -1 for certain subjects to obtain values less than or equal to one in all subjects. [6] In addition to adding variables together to derive an intermediate variable or a diagnosis, multiplication, categorization, and other more complicated methods were used in the diagnostic criteria to generate diagnosis variables and domain variables in the major or minor criteria. For example, the diagnosis of dysthymic disorder required the confirmation of both the major criteria, "depressed mood most of the day for more days than not, for at least 2 years" and the minor criteria, "the presence of two or more of the following symptoms", at the same time. This was the same as multiplying two binomial variables to obtain the diagnosis of dysthymic disorder. Other equations to generate the intermediate variables and the diagnoses were listed and explained in Table 2 to Table 4.

5657150 Generation of bias variables

58151Bias variables were generated while binomial input symptoms were summed or multiplied59152to obtain binomial intermediate or diagnosis variables.[6]Therefore the number of bias variables60

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- depended on the complexity of how the diagnoses were made. For example, six of the nine items or domains in the minor criteria for the diagnosis of major depressive episodes were the censored sums of the input symptoms and six bias variables were derived along with the intermediate variables that represented the items in the minor criteria. The other bias variables were described in Table 2 to Table 4.
- Simulation parameters and simulated populations We simulated populations of 100,000 subjects. There were five prevalence rates to simulate the input symptoms for the diagnosis of major depressive episodes, dysthymic disorder, and manic episodes: 0.05, 0.1, 0.3, 0.5, and 0.7. The correlations between the input symptoms were hypothesized to be 0, 0.1, 0.4, 0.7, and 0.9. There were 25 combinations of the assumed prevalence rates and between-variable correlations. The presence of the input symptoms were randomly assigned to the subjects after specifying the prevalence rates and between-variable correlations between the input symptoms. [20, 21] The intermediate and diagnosis variables were derived according to the equations in Table 2 to Table 4. For each combination of prevalence rates and between-variable correlations, the populations were simulated for 100 times to obtain the mean values and 95% confidence intervals (CIs) of derived prevalence rates, as well as the adjusted R squared and p values to approximate the diagnosis variables.

27 170 Diagnosis approximation 28

Due to the existence of the biases, the input symptoms were not likely to fully explain the diagnoses.[6] Therefore, the diagnoses were approximated by the input, bias, and intermediate variables individually or collectively.[6, 12, 14, 16] The approximation was conducted using forward-stepwise linear regressions. [6, 12, 14, 16, 22] The interpretability of the diagnoses by the input symptoms and bias variables was assessed via adjusted R square: zero suggesting that the input symptoms unrelated to the diagnosis; one suggesting that the input symptoms perfectly explained the diagnosis.[14, 15, 23-26]

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40178All statistical analyses were conducted within R environment (v3.4.1)[27] and RStudio179(v1.0.153).[28] P values less than 0.05 were considered statistical significant, two-tailed.

180 Results

181 The derived prevalence rates of the input symptoms of the three mental illnesses 182 matched the assumed rates in Figure 1. The derived correlations between the input 183 symptoms were close to assumed levels in S 3. The simulations were successful and 184 accurate based on the assumed prevalence rates and correlations.

51 185 Prevalence of intermediate variables

The items in the major and minor criteria were the intermediate variables necessary to create the diagnoses. The methods to generate the intermediate variables were as important to the prevalence rates of the intermediate variables as the prevalence rates and correlations of the input symptoms in Figure 2. The intermediate variable, significant unintentional weight loss or gain, was created by summing and censoring two binomial variables with values of zero and one (significant unintentional weight loss; significant unintentional weight gain). The prevalence rates of the

intermediate variables were larger than those of the two input symptoms regardless of the assumedprevalence rates or between-variable correlations of the input symptoms.

194 In contrast, the diagnosis of dysthymic disorder was a multiplication product of two binomial 195 variables, the major and minor criteria, and the prevalence rates of dysthymic disorder were lower 196 than those of the major and minor criteria under all combinations of assumed correlations and 197 prevalence rates in Figure 3.

1213 198 Prevalence of mental illnesses

The prevalence rates of three diagnoses were plotted against the assumed prevalence rates and correlations of the input symptoms in Figure 3 to Figure 5 and listed in Table 5. None of the three diagnoses had prevalence rates exceeding those of the input symptoms. In general, higher prevalence rates or between-variable correlations of the input symptoms were associated with higher prevalence rates in the three diagnoses, except for manic episodes that had higher prevalence rates (0.692) assuming zero correlations and 0.7 prevalence rates than the prevalence rate (0.679) assuming 0.1 correlations and 0.7 prevalence rates of the input symptoms. When compared across Figure 3 to Figure 5, given the same assumed prevalence rates and between-variable correlations of the input symptoms, the diagnostic criteria of dysthymic disorder consistently generated diagnoses of the highest prevalence rates and the criteria of major depressive episodes created diagnoses of the least prevalence rates (see Table 5 for details).

30 210 Associations between the diagnoses and individual input symptoms and bias

211 variables

The diagnoses were interpreted by the input symptoms (including intermediate variables) and the bias variables individually first. Take dysthymic disorder for example, the diagnosis was interpreted with the input symptoms, the bias variables, and both in Figure 6. For each simulation, the diagnosis of dysthymic disorder was approximated with an increasing number of the input symptoms, the bias variables, or both. After selecting the variables that best approximated the diagnosis based on adjusted R-squared, the input symptoms could explain a proportion of 0.955 of the diagnosis variance and the bias variables could explain at most a proportion of 0.405 of the diagnosis variance in Figure 6. With all variables used in the regression, the diagnosis could be perfectly explained by the input symptoms and bias variables (adjusted R-squared = 1). By repeating the same procedures to the diagnoses, the individual input symptoms and the bias variables that individually best explained the diagnoses were listed in Error! Reference source not found. and Table 7 respectively.

For the diagnosis of major depressive episodes, the first and second items in the major criteria (variable names: mde_ma1 for or mde_ma2 in Table 2) individually explained the diagnosis the best depending on the assumed prevalence rates and correlations in Error! Reference source not found.. For the diagnosis of dysthymic disorder, the major criteria (dys ma in Table 3) consistently and individually explained the diagnosis the best. For the diagnosis of manic episodes, the third item of the major criteria (man_ma3 in Table 4) individually explained the diagnosis the best in all combinations of assumed prevalence rates and correlations. However, the proportions of diagnosis variances best explained by individual input symptoms varied in a large range between 0.001 to 0.974 depending on the assumed prevalence rates and between-variable correlations. Based on the adjusted R-squared for individual input symptoms, certain input variables were more important than other symptoms due to high correlation with the diagnoses, such as the major

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criteria for the diagnosis of dysthymic disorder. The prevalence rates and between-variable correlations were important to determine the relationships between input symptoms and diagnoses. Similarly, there were bias variables that consistently explained the diagnoses the best in Table 7. For the diagnosis of major depressive episodes, the bias due to categorization of the numbers of confirmed input symptoms up to three or four (mde bias1 or mde bias2 respectively in Table 2) were the leading bias variable. The diagnosis of major depressive episodes not explained by the input symptoms or information censoring (mde bias in Table 2) were the leading bias variable in two combinations of the assumed prevalence rates and correlations. For the diagnosis of dysthymic disorder, the residual of the diagnosis not explained by the major and minor criteria (dys_bias in Table 3) and the bias due to categorization of the confirmed input symptoms in the minor criteria (dys mi bias) were the leading bias variables. For the diagnosis of manic episodes, the bias due to categorization of the number of confirmed input symptoms in the minor criteria up to three (man bias1 in Table 4) was the leading bias variables, except for two combinations of the assumed prevalence rates and correlations, in which the bias due to categorization of the confirmed input symptoms in the minor criteria up to four (man bias2 in Table 4) best explained the diagnosis. However, the proportions of diagnosis variances explained by individual bias variables varied in a wide range from zero to 0.87. Depending on the assumed prevalence rates and between-variable correlations of the input symptoms, certain bias variables were more important than other bias variables and even some input variables. The assumed prevalence rates and between-variable correlations were important factors for the relationships between the bias variables and the diagnoses.

In general, the proportions of the diagnosis variances could be explained by either individual input symptoms or single bias variables were low when the prevalence rates and between-variable correlations of the input symptoms were assumed low. With higher assumed prevalence rates or correlations, the proportions of the diagnoses explained by the single input symptoms or bias variables were higher. Across three diagnoses, the diagnosis of dysthymic disorder could be better explained by its own single input variables (higher adjusted R-squared) and the diagnosis of major depressive episodes was associated with the least adjusted R-squared. The bias variables of the diagnosis of manic episodes could explain the diagnosis individually better than the bias variables of the other two diagnoses.

Approximation of the diagnoses with input symptoms

When the diagnoses were approximated with all input symptoms of their own in Table 8, there were always some diagnosis variances that could not be explained by the input symptoms. In other words, the input symptoms could not fully explain the diagnoses, except for the diagnosis of dysthymic disorder that could be fully explained by the input symptoms (adjusted R-squared = 1) assuming zero between-variable correlations and 0.7 prevalence rates for the input symptoms. In Table 8, the proportions of diagnosis variances explained by input symptoms increased with higher assumed prevalence rates or between-variable correlations of the input symptoms in general. The input symptoms of dysthymic disorder explained the diagnosis better than those of the other two diagnoses under all combinations of assumed prevalence rates and between-variable correlations. The diagnosis of major depressive episodes was the worst approximated with its own input symptoms in terms of adjusted R-squared. However, the proportions of diagnosis variances explained by own

input symptoms varied in a wide range between 0.003 to 1.0. The assumed prevalence rates
and between-variable correlations of the input symptoms and the design of the diagnostic
criteria were all important for the relationships between input symptoms and diagnoses.

280 Approximating the diagnoses with bias variables

The diagnoses were approximated with the bias variables of their own. The bias variables always explained some of the diagnosis variances, except for the diagnosis of dysthymic disorder assuming zero between-variable correlations and 0.7 prevalence rates for the input symptoms (adjusted R-squared = 0). With increasing assumed between-variable correlations for the input symptoms, the adjusted R-squared increased. However, given the same assumed between-variable correlations, the proportions of diagnosis variances explained by the bias variables might increase or decrease with the assumed prevalence rates. Compared to the adjusted R-squared in Table 8, the proportions of the diagnosis variances explained by the bias variables were always smaller than those explained by the input symptoms in Table 9. However, the proportions of diagnosis variances explained by bias variables also varied in a wide range from zero to 0.89. The assumed prevalence rates and between-variable correlations of input symptoms and the design of the diagnostic criteria were important for the relationship between the bias variables and the diagnoses. Only when the input symptoms for the diagnosis of dysthymic disorder were randomly and independently prevalent to 70% of the simulated populations, the bias variables became irrelevant to the diagnosis.

31 297 Discussion

This study is the first attempt to understand the relationships between the input symptoms and the diagnoses of three mental illnesses: major depressive episodes (at least one episode required for the diagnosis of major depressive disorder), dysthymic disorder, and manic episodes. The diagnostic criteria of three mental illnesses have been reviewed and rewrote as mathematical functions. Simulated populations, 100,000 for each of 100 simulations, with input symptoms of the three diagnoses were created. For simplicity and practicality reasons, the presence of the input symptoms was randomly assigned and the input symptoms were assumed to have uniform prevalence rates and between-variable correlations. There were 25 combinations of assumed prevalence rates and between-variable correlations simulated.

Mathematically, the diagnostic criteria are functions and composite measures to transform the information from the input variables to diagnoses. There are bias variables created in the process of information transformation.[6] There are three major mechanisms of introducing biases, censoring, data categorization[7] and multiplication of input symptoms with values of zero and one presenting the absence and presence of the symptoms.[6] These mechanisms introduce information or biases that cannot be fully explained by the input symptoms.[6] The biases introduced can sometimes explain more than half of the variances of the diagnoses depending on the prevalence rates and between-variable correlations of the input symptoms (e.g. assuming input symptoms with 0.7 or 0.9 prevalence rates for the three diagnoses). The findings show that the design of the diagnostic criteria important for bias introduction and significant for the prevalence of the diagnoses in populations, the relationships between the input symptoms and the diagnoses, and the relationships between the bias variables and the diagnoses.

The impact of the diagnostic criteria

With the same assumptions in the prevalence rates and between-variable correlations of the input symptoms, the design of the diagnostic criteria of three mental illnesses can be compared to each other. The design of diagnostic criteria transform input symptoms to various diagnosis prevalence rates with implicit upper limits (i.e. no more prevalent than the input symptoms), unacknowledged differential weights on the input symptoms (i.e. certain input symptoms explaining the diagnoses better), and the introduction of biases (i.e. due to censoring, data categorization, or multiplication).

We were the first to notice that the prevalence rates of the three diagnoses were lower than those of the input symptoms, if randomly distributed with uniform prevalence rates and correlations. Given similar assumed input symptom prevalence and correlations, dysthymic disorder is the most prevalent and major depressive episodes are the least. The diagnosis of dysthymic disorder can be better explained by own input symptoms individually or collectively. The diagnosis of major depressive episodes is the worst explained by own input symptoms individually or collectively. As expected, the diagnosis of the three mental illness are similar to composite measures or indices and are subject to the biases introduced by data processing given all combinations of the assumed prevalence rates and between-variable correlations of the input symptoms.[6] There is only one exception: dysthymic disorder with the input symptoms that are randomly and independently present in 70% of the population. This is because the diagnosis of dysthymic disorder is a multiplication product of the major and minor criteria. Without correlations, everyone in the population is certain to qualify for the minor criteria (probability of 100% because of having at least two out of six item in the minor criteria: mathematically [C(2,6) + C(3,6) + C(4,6) + C(5,6) + C(6,6)] X $(0.7)^6$) = 37 X 0.117 = 4.35 > 100%). When 70% of the population are also randomly assigned with the major criteria, the diagnosis of dysthymic disorder can be fully explained by the major criteria alone. In fact, without correlations between input symptoms it only requires each of the six items in the minor criteria to be randomly assigned to 54.8% $[(1/37)^{(1/6)}]$ of the population for everyone to qualify for the minor criteria and the diagnosis can be fully explained by the minor and major criteria.

Distortion of the input symptoms

The importance of the input symptoms has been distorted due to the functions to generate the diagnoses. This has been proven in the diagnosis of frailty.[6] In other words, based on the functions to generate the diagnoses, the input symptoms are differentially weighted without the weights being explicitly acknowledged. The most prominent is the diagnosis of dysthymic disorder, more than 90% of whose variance can be explained by its major criteria assuming 0.7 or 0.9 between-variable correlations for the input symptoms in Table 6. Another example is that the third item of the major criteria for the diagnosis of manic episodes, "irritable mood", individually predicts the diagnosis better than any other input symptoms. Assuming 0.9 correlations between input symptoms, this input symptom has been put more weight than others and can explain more than 91.8% of the diagnosis variance. Based on the texts in the DSM-IV-TR, we don't think this symptom should be emphasized to this degree and consider the diagnostic criteria are imposing implicit and unequal weights to the input symptoms, as well as introducing biases.

Future directions

We think it important to rethink the role and importance of the diagnostic system. Current approaches are embedded with implicit assumptions of the prevalence rates of the diagnoses (no higher than input symptoms), unacknowledged weights to input symptoms (certain input symptoms explaining the diagnoses much better), and biases that could not be explained by the input symptoms. The diagnosis of dysthymic disorder is probably accidentally "designed" to be more prevalent than that of major depressive episodes or manic episodes based on the diagnostic criteria assuming input symptoms with the same prevalence rates. In the real world, there are other important issues related to the diagnostic criteria. For example, diagnosis is not closely linked to treatment, [19, 29] diagnosis is not well made particularly by non-psychiatrists, [30] and there are two diagnostic systems (DSM and International Classification of Disease) that require efforts to harmonize.[31] Amid these issues, we think the diagnostic criteria for mental illnesses should be reviewed and improved in a way that they can be easier to understand and use without introducing biases and can be closely linked to clinical decisions. We are developing methods to better detect symptom-based conditions and proposing methods to search for neglected mental symptoms.

Limitations

The strength of this study is the use of simple assumptions in simulated populations that enables the comparison of the diagnostic criteria of three mental illnesses. However, the assumptions in the prevalence rates and between-variable correlations for the input symptoms might not be realistic. Some of the assumptions are unlikely to hold in the real world. However, this is the only option for us due to the lack of real-world data on the prevalence of the input symptoms. In addition, the translation from symptoms to diagnoses was assumed to be perfect based on the diagnostic criteria.

Conclusion

To the best of our knowledge, there is no study on the relationships between the input symptoms and the diagnoses. The input symptoms were extracted from the diagnostic criteria and the diagnostic criteria were transformed to mathematical equations. Without mental illness data available to the public, 100,000 subjects were simulated with different assumptions on the prevalence rates (0.05, 0.1, 0.3, 0.5, and 0.7) and correlations (0, 0.1, 0.4, 0.7, and 0.9) of the input symptoms. We found that biases were introduced to the diagnoses of three mental illnesses, major depressive episodes, dysthymic disorder, and manic episodes. The prevalence rates of the diagnoses were proportional to the assumed prevalence rates and between-variable correlations of the input symptoms. Certain input symptoms were more important than the others to explain the diagnoses. However, the input symptoms could not fully explain the diagnoses, except when the input symptoms independent to each other with 0.7 prevalence rates were used for the diagnosis of dysthymic disorder.

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3 ⊿	402	Declarations
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6	403	Patient and Public Involvement
7 8	404	This is a simulation study that does not require the input from patients or the public.
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11	406	Not applicable.
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23	413	Consent for publication
25	414	Not applicable
26		
27	415	Data Availability
28	416	No real-world data used. All analysis based on simulations reproducible with the files in the
29 30	417	Supplemental materials
31	117	
32	418	Competing Interests
33	419	YSC is currently employed by the Canadian Agency for Drugs and Technologies in Health
34 25	420	The other authors have declared that no competing interests exist
35 36	420	
37	421	Authors' Contributions
38	422	YSC concentualized and designed this study, managed and analyzed data and drafted the
39	122	manuscript. KEL assisted in the interpretation of the diagnostic criteria. CIW assisted in data
40	423	manuscript. Ki assisted in the interpretation of the diagnostic criteria. Give assisted in data
41 42	424	management and computation. HCW, HTH, LCT, YPC, YCL, and WCC participated in the design of this
43	425	study. All authors reviewed and approved the manuscript.
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512 Table 1. The assumptions and parameters in the simulations	
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	Assumptions		
1	Equal prevalence rates for the input symptoms of the same diagnosis; presence of input symptoms assigned randomly		
2	Same correlations between the input symptoms of the diagnoses of major depressive episodes and dysthymic disorder; same correlations between the input symptoms of manic episodes		
3	The input symptoms of manic episodes created independent of those of major depressive episodes and dysthymic disorder		
4	Diagnoses made accurately based on the diagnostic criteria and symptoms reported accurately by patients		
	Parameters of input symptoms of the same diagnosis for each simulation		
1	Population sizes	10,000	
2	Prevalence rates (uniform for all input symptoms in a simulation)	0.05, 0.1, 0.3, 0.5, and 0.7	
3	Correlations (uniform between all input symptoms of the same diagnosis in a simulation)	0, 0.1, 0.4, 0.7, and 0.9	
4	Number of simulations for each combination of the assumed prevalence rates and between-variable correlations of the input symptoms	100	

519 Table 2. The input symptoms, intermediate variables, and bias variables for the diagnosis of major depressive episodes.

classification of symptoms	variable	or minor criteria	variables	Symptoms	variables	Equations to derive diagnosis or domain variables	Approximation by linear regression	wechanisms related to introducing blases
Major depressive episode (variable = mde)						<pre>mde = mde_ma1 x mde_ma2 x (mde_mi3 + mde_mi4 + mde_mi5 + mde_mi6 + mde_mi7 + mde_mi8 + mde_mi9 + mde_bias1) + (1- mde_ma1 x mde_ma2) x (me_ma1 x mde_ma2) x (mde_mi3 + mde_mi4 + mde_mi5 + mde_mi6 + mde_mi7 + mde_mi8 + mde_mi9 + mde_bias2)</pre>	mde = intercept + coef1 x mde_ma1 + coef2 x mde_ma2 + coef3 x mde_mi3 + coef4 x mde_mi4 + coef5 x mde_mi5 + coef6 x mde_mi6 + coef7 x mde_mi7 + coef8 x mde_mi8 + coef9 x mde_mi9 + coef10 x mde_bias	 Multiplication to create the situat one or two symptoms in the majo confirmed and the bias (mde_bias calculated by extracting the inforr the diagnosis not explained by the symptoms and two bias variables by censoring (mde_bias1 and mde 2) Categorizing of the sum of the inp symptoms in the minor criteria at threshold of three or four (mde_bias2)
Major criteria, essential for diagnosis								
		Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks.						
		Depressed mood for more than two weeks.	mde_ma1					
		Loss of interest or pleasure in daily activities for more than two weeks.	mde_ma2					
Minor criteria (at least 5 of the symptoms including the two in major criteria)	mde_mi							
		Significant unintentional weight loss or gain	mde_mi3			mde_mi3 = mde_mi3_1 + mde_mi3_2 + mde_mi3_bias		Censoring of the sum of multiple input variables
				Significant unintentional weight gain	mde_mi3_1			
				Significant unintentional weight loss	mde_mi3_2			
				Information of the domain not explained by the input variables	mde_mi3_bias			
		Insomnia or sleeping too much\$	mde_mi4			mde_mi4 = mde_mi4_1 + mde_mi4_2 + mde_mi4_bias		Censoring of the sum of multiple input variables
				Insomnia	mde_mi4_1			
				Sleeping too much Information of the domain not explained by the input variables	mde_mi4_2 mde_mi4_bias			
		Agitation or psychomotor retardation noticed by others	mde_mi5	input vondores		mde_mi5 = mde_mi5_1 + mde_mi5_2 + mde_mi5_bias		Censoring of the sum of multiple input variables
				Agitation	mde mi5 1			

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					Psychomotor	mde_mi5_2			
					by others				
					Information of the	mde_mi5_bias			
					domain not				
					explained by the input variables				
			Fatigue or loss of	mde_mi6			mde_mi6 = mde_mi6_1 + mde_mi6_2 +		Censoring of the sum of multiple input variables
			energy			1 10 4	mde_mi6_bias		
					Fatigue Loss of energy	mde_mi6_1			
					Information of the	mde_mi6_bias			
					domain not				
					explained by the input variables				
			Feelings of	mde_mi7	input vanables		mde_mi7 = mde_mi7_1 + mde_mi7_2 +		Censoring of the sum of multiple input variables
			worthlessness or				mde_mi7_bias		
			excessive guilt		Feelings of	mde mi7 1			
					worthlessness				
					Feelings of	mde_mi7_2			
					Information of the	mde mi7 bias			
					domain not				
					explained by the				
			Diminished ability to	mde_mi8	input vanabies		mde_mi8 = mde_mi8_1 + mde_mi8_2 +		Censoring of the sum of multiple input variables
			think or concentrate, or indecisiveness+				mde_mi8_bias		
					Diminished ability	mde_mi8_1			
					concentrate				
					Indecisiveness	mde_mi8_2			
					Information of the domain not	mde_mi8_bias			
					explained by the				
			Desurrent thoughts of	mada mi0	input variables				
			death	Inde_Inia					
	Information due to	mde_bias1							Bias introduced to categorize the sum of the number of
	categorization (choosing three								confirmed symptoms in the minor criteria
	domains in minor								
	criteria)	mada bias2							Discipture durand the enterprise the sums of the sumshare of
	categorization	mde_blasz							confirmed symptoms in the minor criteria
	(choosing four								
	domains in minor								
	Information of	mde bias							Information of the diagnosis not explained by the input
	diagnosis not	_							variables and two bias variables generated due to data
	explained by the								categorization
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523 Table 3. The input symptoms, intermediate variables, and bias variables for the diagnosis of dysthymic disorder.

Classification of symptoms	Criterion variable	Major or minor criteria (domains)	Intermediate variables	Symptoms	Symptom variables	Equations to generate diagnosis or domain variables	Approximation	Mechanisms related to introducing biases
Dysthymia (variable = dys)						dys = dys_ma x dys_mi	dys = intercept + coef1 x dys_ma + coef2 x dys_mi + coef3 x dys_bias	Multiplication to create the situations where both the major and minor criteria met (union of two binomial variables, mde_ma x mde_mi) and the bias variable (dys_bias) equivalent to the residual of the diagnosis not explained by the input symptoms and the bias variables due to censoring and categorization
Major criteria, essential for diagnosis								
		Depressed mood most of the day for more days than not, for at least 2 years	dys_ma					
Minor criteria (at least 2 items)			dys_mi			dys_mi = dys_mi1 + dys_mi2 + dys_mi3 + dys_mi4 + dys_mi5 + dys_mi6 + dys_mi_bias		Categorizing of the sum of multiple input variables
		Poor appetite or overeating	dys_mi1			dys_mi1 = dys_mi1_1 + dys_mi1_2 + dys_mi1_bias		Censoring of the sum of multiple input variables
				Poor appetite	dys_mi1_1			
				Overeating	dys_mi1_2			
				Information of the domain not explained by the input variables	dys_mi1_bias			
		Insomnia or sleeping too much*	dys_mi2/mde_mi4			dys_mi2 = mde_mi4 = mde_mi4_1 + mde_mi4_2 + mde_mi4_bias		Censoring of the sum of multiple input variables
				Insomnia Sleeping too much	mde_mi4_1 mde_mi4_2			
				Information of the domain not explained by the input variables	mde_mi4_bias			
		Low energy or fatigue*	dys_mi3/mde_mi6			dys_mi3 = mde_mi6 = mde_mi6_1 + mde_mi6_2 + mde_mi6_bias		Censoring of the sum of multiple input variables
				Fatigue	mde_mi6_1			
				Loss of energy (low energy)	mde_mi6_2			
				Information of the domain not explained by the input variables	mde_mi6_bias			
		Low self-esteem	dys_mi4					
		Poor concentration or difficulty making decisions*	dys_mi5/mde_mi8			dys_mi5 = mde_mi8 = mde_mi8_1 + mde_mi8_2 + mde_mi8_bias		Censoring of the sum of multiple input variables
				Diminished ability to think or concentrate (Poor concentration)	mde_mi8_1			
				difficulty making decisions (indecisiveness)	mde_mi8_2			
					made million			
				domain not explained by the the input variables	mde_mi8_blas			

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2 3 4				Information of minor criteria not explained by	dys_mi_bias	Bias introduced by categorizing the number of input symptoms confirmed in the minor criteria
5 6 7		Information of diagnosis not explained by major or minor criteria	dys_bias	input variables		Information of the diagnosis not explained by the input symptoms and the bias variables generated due to data categorization (dys_mi_bias)
/ 8	524	*The same inpu	ut sympto	ms used for the	diagnosis of major depressive episodes.	
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527 Table 4. The input symptoms, intermediate variables, and bias variables for the diagnosis of manic episodes.

symptoms	variable	iviajor or minor criteria (domains)	variables	symptoms	symptom variables	Equations	Approximation	Mechanisms related to introducing blases
Manic episode (variable = manic)						<pre>manic = (1- man_ma1 x man_ma2) x (man_ma1 + man_ma2) x man_ma3 x (man_mi1 + man_mi2 + man_mi3 + man_mi4 + man_mi5 + man_mi6 + man_mi7 + man_bias1) + [1 - (1 - man_ma1 x man_ma2)(man_ma1 + man_ma2)] x man_ma3 x (man_mi1 + man_mi2 + man_mi3 + man_mi4 + man_mi5 + man_mi6 + man_mi7 + man_bias2)</pre>	 manic = intercept + coef1 x man_ma1 + coef2 x man_ma2 + coef3 x man_ma3 + coef4 x man_mi1 + coef5 x man_mi2 + coef6 x man_mi3 + coef7 x man_mi4 + coef8 x man_mi5 + coef9 x man_mi6 + coef10 x man_mi7 + coef11 x man_bias 	 Multiplication to create the situations where one of the symptom in the major criter met (union of three binomia variables, such as man_ma1 man_ma2 and man_ma1 x man_ma2), \n multiplication for the condition of presenting irritable mood (x man_ma3), and the bias variable (man_bias) equivalent to the residual of the diagnosis not explained I the input symptoms and the bias variables due to censoring; the bias variables introduced by categorizing the number - input symptoms confirmed i the minor criteria (man_bias) and man_bias (2)
Major criteria, essential								and man_blas2)
or the diagnosis of a nanic episode (more than one bipolar episode required to diagnose bipolar disorder)								
		A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)						
				Elevated mood, lasting at least 1 week	man_ma1			
				Expansive mood, lasting at least 1 week	man_ma2			
				Irritable mood, lasting at least 1 week	man_ma3			
Minor criteria (3 or more of the following symptoms have persisted; 4 if the mood is only irritable)								
		Increased self-esteem or grandiosity	man_mi1			man_mi1 = man_mi1_1 + man_mi1_2 + man_mi1_bias		Censoring of the sum of multiple input variables
				Increased self- esteem	man_mi1_1			
				Grandiosity	man mi1 2			
				Information of the domain not explained by the	man_mi1_bias			

		Decreased need for sleep (e.g., feels rested after only 3 hours	man_mi2				
		of sleep)					
		More talkative than usual or pressure to keep talking	man_mi3			man_mi3 = man_mi3_1 + man_mi3_2 + man_mi3_bias	Censoring of the sum of multiple input variables
				More talkative than usual	man_mi3_1		
				Pressure to keep	man_mi3_2		
				Information of the domain not explained by the	man_mi3_bias		
		Flight of ideas or subjective experience that thoughts are racing	man_mi4	input variables		man_mi4 = man_mi4_1 + man_mi4_2 + man_mi4_bias	Censoring of the sum of multiple inpu variables
				Flight of ideas	man_mi4_1		
				subjective experience that thoughts are racing	man_mi4_2		
				Information of the domain not explained by the input variables	man_mi4_bias		
		Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)	man_mi5				
		Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation	man_mi6			man_mi6 = man_mi6_1 + man_mi6_2 + man_mi6_bias	Censoring of the sum of multiple inpu variables
				Increase in goal- directed activity	man_mi6_1		
				Psychomotor	man_mi6_2		
				Information of the domain not explained by the input variables	man_mi6_bias		
		Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)"	man_mi7				
nformation of diagnosis due to categorization choosing at least three symptoms)	man_bias1						Bias introduced by categorizing the n of input symptoms confirmed in the r criteria
nformation of diagnosis due to categorization choosing at least four symptoms)	man_bias2						Bias introduced by categorizing the n of input symptoms confirmed in the r criteria
Information of diagnosis not explained by symptoms	man_bias						Information of the diagnosis not expl. by the input symptoms and the bias variables generated due to data categorization.man bias1 and man

Table 5. The derived prevalence rates of the diagnoses of major depressive episodes, dysthymic disorder, and manic episodes based on the assumed prevalence rates and between-variable correlations of the input symptoms

0.05 0.1 0.3 0.5 0.7 0.05	0 (95% CI = 0 to 0) 0.001 (95% CI = 0.001 to 0.001) 0.067 (95% CI = 0.067 to 0.067) 0.245 (95% CI = 0.244 to 0.245) 0 49 (95% CI = 0.49 to 0.49)	0.004 (95% Cl = 0.004 to 0.004) 0.025 (95% Cl = 0.025 to 0.025) 0.249 (95% Cl = 0.249 to 0.249) 0.493 (95% Cl = 0.493 to 0.493)	0 (95% Cl = 0 to 0) 0.002 (95% Cl = 0.002 to 0.002) 0.136 (95% Cl = 0.135 to 0.136)
0.1 0.3 0.5 0.7 0.05	0.001 (95% CI = 0.001 to 0.001) 0.067 (95% CI = 0.067 to 0.067) 0.245 (95% CI = 0.244 to 0.245) 0.49 (95% CI = 0.49 to 0.49)	0.025 (95% CI = 0.025 to 0.025) 0.249 (95% CI = 0.249 to 0.249) 0.493 (95% CI = 0.493 to 0.493)	0.002 (95% CI = 0.002 to 0.002) 0.136 (95% CI = 0.135 to 0.136)
0.3 0.5 0.7 0.05	0.067 (95% CI = 0.067 to 0.067) 0.245 (95% CI = 0.244 to 0.245) 0.49 (95% CI = 0.49 to 0.49)	0.249 (95% Cl = 0.249 to 0.249) 0.493 (95% Cl = 0.493 to 0.493)	0.136 (95% CI = 0.135 to 0.136)
0.5 0.7 0.05	0.245 (95% Cl = 0.244 to 0.245) 0 49 (95% Cl = 0 49 to 0 49)	0.493 (95% CI = 0.493 to 0.493)	
0.7 0.05	(0.49)(95%)(1 = (0.49)(0.49))		0.436 (95% CI = 0.436 to 0.436)
0.05		0.7 (95% Cl = 0.7 to 0.7)	0.692 (95% CI = 0.692 to 0.693)
0.1	0.004 (95% Cl = 0.004 to 0.004)	0.018 (95% Cl = 0.018 to 0.018)	0.007 (95% Cl = 0.007 to 0.007)
0.1	0.011(95% Cl = 0.011 to 0.011)	0.049 (95% CI = 0.049 to 0.049)	0.022 (95% Cl = 0.021 to 0.022)
0.3	0.094 (95% Cl = 0.094 (0.094) 0.267 (95% Cl = 0.267 to 0.268)	0.25(95% CI = 0.25(0.0.25)) 0.482(95% CI = 0.482 to 0.482)	0.172 (95% Cl = 0.171 (0.0.172) 0.425 (95% Cl = 0.425 to 0.425)
0.3	0.207 (95% Cl = 0.207 (0.0.208)	0.482(95% Cl = 0.482(0.0.482) 0.697(95% Cl = 0.697 to 0.697)	0.423 (95% Cl = 0.423 to 0.423)
0.05	0.019(95% Cl = 0.019 to 0.019)	0.037 (95% Cl = 0.037 to 0.037)	0.029 (95% Cl = 0.029 to 0.029)
0.05	0.042 (95% Cl = 0.042 to 0.042)	0.037 (95% Cl = 0.037 to 0.037)	0.023 (95% Cl = 0.023 to 0.023)
0.1	0.166(95% Cl = 0.166 to 0.167)	0.267 (95% Cl = 0.267 to 0.267)	0.231 (95% Cl = 0.231 to 0.231)
0.5	0.344 (95% Cl = 0.344 to 0.344)	0.476 (95% Cl = 0.476 to 0.476)	0.44 (95% Cl = 0.44 to 0.441)
0.7	0.57 (95% Cl = 0.57 to 0.57)	0.689 (95% Cl = 0.688 to 0.689)	0.666 (95% Cl = 0.666 to 0.666)
0.05	0.035 (95% CI = 0.035 to 0.035)	0.046 (95% CI = 0.046 to 0.046)	0.042 (95% CI = 0.042 to 0.042)
0.1	0.071 (95% CI = 0.071 to 0.071)	0.092 (95% CI = 0.092 to 0.092)	0.085 (95% CI = 0.085 to 0.085)
0.3	0.233 (95% CI = 0.233 to 0.234)	0.285 (95% CI = 0.285 to 0.285)	0.27 (95% CI = 0.27 to 0.27)
0.5	0.422 (95% CI = 0.421 to 0.422)	0.486 (95% CI = 0.485 to 0.486)	0.469 (95% CI = 0.468 to 0.469)
0.7	0.635 (95% CI = 0.635 to 0.635)	0.69 (95% CI = 0.69 to 0.691)	0.678 (95% CI = 0.677 to 0.678)
0.05	0.042 (95% CI = 0.042 to 0.042)	0.048 (95% CI = 0.048 to 0.048)	0.046 (95% CI = 0.046 to 0.046)
0.1	0.085 (95% CI = 0.085 to 0.085)	0.096 (95% CI = 0.096 to 0.097)	0.093 (95% CI = 0.093 to 0.093)
0.3	0.268 (95% CI = 0.268 to 0.268)	0.293 (95% CI = 0.293 to 0.293)	0.286 (95% CI = 0.286 to 0.287)
0.5	0.463 (95% CI = 0.463 to 0.463)	0.493 (95% CI = 0.492 to 0.493)	0.485 (95% CI = 0.485 to 0.486)
0.7	0.669 (95% CI = 0.669 to 0.669)	0.695 (95% CI = 0.694 to 0.695)	0.688 (95% CI = 0.688 to 0.688)
	0.1 0.3 0.5 0.7 0.05 0.1 0.3 0.5 0.7 0.05 0.1 0.3 0.5 0.7	0.1 0.042 (95% CI = 0.042 to 0.042) 0.3 0.166 (95% CI = 0.166 to 0.167) 0.5 0.344 (95% CI = 0.344 to 0.344) 0.7 0.57 (95% CI = 0.57 to 0.57) 0.05 0.035 (95% CI = 0.035 to 0.035) 0.1 0.071 (95% CI = 0.071 to 0.071) 0.3 0.233 (95% CI = 0.233 to 0.234) 0.5 0.422 (95% CI = 0.421 to 0.422) 0.7 0.635 (95% CI = 0.035 to 0.635) 0.05 0.042 (95% CI = 0.042 to 0.042) 0.1 0.085 (95% CI = 0.085 to 0.085) 0.3 0.268 (95% CI = 0.268 to 0.268) 0.5 0.463 (95% CI = 0.669 to 0.669) 0.7 0.669 (95% CI = 0.669 to 0.669)	0.1 0.042 (95% CI = 0.042 to 0.042) 0.078 (95% CI = 0.078 to 0.078) 0.3 0.166 (95% CI = 0.344 to 0.344) 0.476 (95% CI = 0.476 to 0.476) 0.5 0.344 (95% CI = 0.37 to 0.57) 0.689 (95% CI = 0.476 to 0.476) 0.05 (95% CI = 0.035 to 0.035) 0.046 (95% CI = 0.046 to 0.046) 0.1 0.071 (95% CI = 0.031 to 0.071) 0.092 (95% CI = 0.092 to 0.092) 0.3 0.233 (95% CI = 0.233 to 0.234) 0.285 (95% CI = 0.285 to 0.285) 0.5 0.422 (95% CI = 0.421 to 0.422) 0.486 (95% CI = 0.485 to 0.486) 0.7 0.635 (95% CI = 0.035 to 0.035) 0.69 (95% CI = 0.485 to 0.486) 0.7 0.635 (95% CI = 0.085 to 0.085) 0.096 (95% CI = 0.048 to 0.048) 0.1 0.085 (95% CI = 0.085 to 0.285) 0.096 (95% CI = 0.091 to 0.691) 0.05 0.042 (95% CI = 0.268 to 0.268) 0.293 (95% CI = 0.293 to 0.293) 0.5 0.463 (95% CI = 0.268 to 0.268) 0.293 (95% CI = 0.293 to 0.293) 0.5 0.463 (95% CI = 0.669 to 0.669) 0.695 (95% CI = 0.694 to 0.695) 0.7 0.669 (95% CI = 0.669 to 0.669) 0.695 (95% CI = 0.694 to 0.695)

534 Table 6. The individual input symptoms that best explained the diagnoses: major depressive episodes, dysthymic

535 disorder, and manic episodes

0.05 0.05 0.1 0.3 0.3 0.5 0.5 0.7 0.7 0.7 0.7 0.05 0.1 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.7 0.7 0.7 0.3 0.3 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	mde_ma1 0.001 (95% CI = 0.001 to 0.001) mde_ma1 0.01 (95% CI = 0.01 to 0.01) mde_ma1 0.167 (95% CI = 0.167 to 0.167) mde_ma2 0.324 (95% CI = 0.324 to 0.325) mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma2 0.07 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	dys_ma 0.076 (95% CI = 0.075 to 0.077) dys_ma 0.228 (95% CI = 0.227 to 0.229) dys_ma 0.774 (95% CI = 0.773 to 0.774) dys_ma 0.971 (95% CI = 0.971 to 0.971) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	man_ma3 0.002 (95% CI = 0.002 to 0.00 man_ma3 0.021 (95% CI = 0.02 to 0.02: man_ma3 0.366 (95% CI = 0.366 to 0.30 man_ma3 0.773 (95% CI = 0.772 to 0.77 man_ma3 0.964 (95% CI = 0.964 to 0.96 man_ma3 0.136 (95% CI = 0.135 to 0.13 man_ma3 0.199 (95% CI = 0.198 to 0.19 man_ma3 0.483 (95% CI = 0.483 to 0.48 man_ma3 0.74 (95% CI = 0.74 to 0.741)
0.05 0.1 0.3 0.3 0.5 0.5 0.7 0.7 0.7 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5	0.001 (95% CI = 0.001 to 0.001) mde_ma1 0.01 (95% CI = 0.01 to 0.01) mde_ma1 0.167 (95% CI = 0.167 to 0.167) mde_ma2 0.324 (95% CI = 0.324 to 0.325) mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma1 0.101 (95% CI = 0.07 to 0.071) mde_ma2 0.242 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0.076 (95% CI = 0.075 to 0.077) dys_ma 0.228 (95% CI = 0.227 to 0.229) dys_ma 0.774 (95% CI = 0.773 to 0.774) dys_ma 0.971 (95% CI = 0.971 to 0.971) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	0.002 (95% CI = 0.002 to 0.00 man_ma3 0.021 (95% CI = 0.02 to 0.02; man_ma3 0.366 (95% CI = 0.366 to 0.36 man_ma3 0.773 (95% CI = 0.772 to 0.77 man_ma3 0.964 (95% CI = 0.964 to 0.96 man_ma3 0.136 (95% CI = 0.135 to 0.13 man_ma3 0.483 (95% CI = 0.198 to 0.48 man_ma3 0.74 (95% CI = 0.74 to 0.741)
0.1 0.3 0.3 0.5 0.5 0.7 0.7 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.05 0.05 0.05	mde_ma1 0.01 (95% CI = 0.01 to 0.01) mde_ma1 0.167 (95% CI = 0.167 to 0.167) mde_ma2 0.324 (95% CI = 0.324 to 0.325) mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma2 0.07 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.365 (95% CI = 0.445 to 0.446) mde_ma1	dys_ma 0.228 (95% CI = 0.227 to 0.229) dys_ma 0.774 (95% CI = 0.773 to 0.774) dys_ma 0.971 (95% CI = 0.971 to 0.971) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	man_ma3 0.021 (95% CI = 0.02 to 0.02 man_ma3 0.366 (95% CI = 0.366 to 0.31 man_ma3 0.773 (95% CI = 0.772 to 0.73 man_ma3 0.964 (95% CI = 0.964 to 0.90 man_ma3 0.136 (95% CI = 0.135 to 0.13 man_ma3 0.483 (95% CI = 0.198 to 0.43 man_ma3 0.74 (95% CI = 0.74 to 0.741)
0.1 0.3 0.5 0.5 0.7 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.5 0.05	0.01 (95% CI = 0.01 to 0.01) mde_ma1 0.167 (95% CI = 0.167 to 0.167) mde_ma2 0.324 (95% CI = 0.324 to 0.325) mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma2 0.07 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0.228 (95% CI = 0.227 to 0.229) dys_ma 0.774 (95% CI = 0.773 to 0.774) dys_ma 0.971 (95% CI = 0.971 to 0.971) dys_ma 0.999 (95% CI = 0.999 to 0.999) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	0.021 (95% CI = 0.02 to 0.02: man_ma3 0.366 (95% CI = 0.366 to 0.31 man_ma3 0.773 (95% CI = 0.772 to 0.73 man_ma3 0.964 (95% CI = 0.964 to 0.94 man_ma3 0.136 (95% CI = 0.135 to 0.13 man_ma3 0.199 (95% CI = 0.198 to 0.14 man_ma3 0.483 (95% CI = 0.483 to 0.44 man_ma3 0.74 (95% CI = 0.74 to 0.741)
0.3 0.5 0.5 0.7 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.5 0.5 0.5 0.05 0.0	mde_ma1 0.167 (95% CI = 0.167 to 0.167) mde_ma2 0.324 (95% CI = 0.324 to 0.325) mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma2 0.07 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.325 (05% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	dys_ma 0.774 (95% CI = 0.773 to 0.774) dys_ma 0.971 (95% CI = 0.971 to 0.971) dys_ma 0.999 (95% CI = 0.999 to 0.999) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	man_ma3 0.366 (95% CI = 0.366 to 0.31 man_ma3 0.773 (95% CI = 0.772 to 0.77 man_ma3 0.964 (95% CI = 0.964 to 0.964 man_ma3 0.136 (95% CI = 0.135 to 0.135 man_ma3 0.199 (95% CI = 0.198 to 0.145 man_ma3 0.483 (95% CI = 0.483 to 0.485 man_ma3 0.74 (95% CI = 0.74 to 0.741)
0.3 0.5 0.5 0.7 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.05 0.05	0.167 (95% CI = 0.167 to 0.167) mde_ma2 0.324 (95% CI = 0.324 to 0.325) mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma2 0.7 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0.774 (95% CI = 0.773 to 0.774) dys_ma 0.971 (95% CI = 0.971 to 0.971) dys_ma 0.999 (95% CI = 0.999 to 0.999) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	0.366 (95% CI = 0.366 to 0.3 man_ma3 0.773 (95% CI = 0.772 to 0.7 man_ma3 0.964 (95% CI = 0.964 to 0.9 man_ma3 0.136 (95% CI = 0.135 to 0.1 man_ma3 0.199 (95% CI = 0.198 to 0.1 man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.5 0.7 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.05 0.05	mde_ma2 0.324 (95% CI = 0.324 to 0.325) mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma2 0.07 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.425 (95% CI = 0.445 to 0.446)	dys_ma 0.971 (95% CI = 0.971 to 0.971) dys_ma 0.999 (95% CI = 0.999 to 0.999) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	man_ma3 0.773 (95% CI = 0.772 to 0.7 man_ma3 0.964 (95% CI = 0.964 to 0.9 man_ma3 0.136 (95% CI = 0.135 to 0.1 man_ma3 0.199 (95% CI = 0.198 to 0.1 man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.5 0.7 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.05 0.05	0.324 (95% CI = 0.324 to 0.325) mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma2 0.07 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0.971 (95% CI = 0.971 to 0.971) dys_ma 0.999 (95% CI = 0.999 to 0.999) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	0.773 (95% CI = 0.772 to 0.7 man_ma3 0.964 (95% CI = 0.964 to 0.9 man_ma3 0.136 (95% CI = 0.135 to 0.1 man_ma3 0.199 (95% CI = 0.198 to 0.1 man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.7 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.05 0.05	mde_ma2 0.412 (95% CI = 0.412 to 0.412) mde_ma2 0.07 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446)	0,999 (95% CI = 0.999 to 0.999) dys_ma 0.353 (95% CI = 0.352 to 0.355) dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	man_ma3 0.964 (95% CI = 0.964 to 0.9 man_ma3 0.136 (95% CI = 0.135 to 0.1 man_ma3 0.199 (95% CI = 0.198 to 0.1 man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.05 0.05 0.1 0.1 0.3 0.3 0.3 0.5 0.5 0.7 0.7 0.7 0.05 0.05 0.05	0.412 (95% CI = 0.412 to 0.412) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0.395 (95% CI = 0.395 (0.395) dys_ma 0.462 (95% CI = 0.352 to 0.355) dys_ma 0.777 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	0.964 (95% CI = 0.964 (0 0.9 man_ma3 0.136 (95% CI = 0.135 to 0.1 man_ma3 0.199 (95% CI = 0.198 to 0.1 man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.05 0.05 0.1 0.3 0.3 0.3 0.5 0.5 0.7 0.7 0.7 0.7 0.05 0.05 0.05	Inde_Ind2 0.07 (95% CI = 0.07 to 0.071) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0,353 (95% Cl = 0.352 to 0.355) dys_ma 0.462 (95% Cl = 0.461 to 0.463) dys_ma 0.777 (95% Cl = 0.777 to 0.778) dys_ma 0.932 (95% Cl = 0.931 to 0.932) dys_ma	0.136 (95% CI = 0.135 to 0.1 man_ma3 0.199 (95% CI = 0.198 to 0.1 man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.03 0.1 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.05 0.05 0.05	0.07 (55% CI = 0.07 (60.071)) mde_ma1 0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	dys_ma 0.462 (95% CI = 0.461 to 0.463) dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	man_ma3 0.199 (95% CI = 0.198 to 0.1 man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.1 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.7 0.05 0.05 0	0.101 (95% CI = 0.1 to 0.101) mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0.462 (95% Cl = 0.461 to 0.463) dys_ma 0.777 (95% Cl = 0.777 to 0.778) dys_ma 0.932 (95% Cl = 0.931 to 0.932) dys_ma	0.199 (95% CI = 0.198 to 0.1 man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.3 0.3 0.5 0.5 0.7 0.7 0.7 0.05 0.05 0.05	mde_ma2 0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	dys_ma 0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	man_ma3 0.483 (95% CI = 0.483 to 0.4 man_ma3 0.74 (95% CI = 0.74 to 0.741
0.3 0.5 0.5 0.7 0.7 0.05 0.05 0.05	0.242 (95% CI = 0.242 to 0.243) mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0.777 (95% CI = 0.777 to 0.778) dys_ma 0.932 (95% CI = 0.931 to 0.932) dys_ma	0.483 (95% Cl = 0.483 to 0.4 man_ma3 0.74 (95% Cl = 0.74 to 0.741
0.5 0.5 0.7 0.7 0.05 0.05 0.1	mde_ma2 0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	dys_ma 0.932 (95% Cl = 0.931 to 0.932) dys_ma	man_ma3 0.74 (95% Cl = 0.74 to 0.741
0.5 0.7 0.7 0.05 0.05 0.1	0.365 (95% CI = 0.365 to 0.366) mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	0.932 (95% Cl = 0.931 to 0.932) dys_ma	0.74 (95% CI = 0.74 to 0.741
0.7 0.7 0.05 0.05 0.1	mde_ma2 0.445 (95% CI = 0.445 to 0.446) mde_ma1	dys_ma	
0.7 0.05 0.05 0.1	0.445 (95% CI = 0.445 to 0.446) mde_ma1		man_ma3
0.05 0.05 0.1	mde_ma1	0.986 (95% CI = 0.986 to 0.986)	0.906 (95% CI = 0.906 to 0.9
0.05 0.1		dys_ma	man_ma3
0.1	0.375 (95% CI = 0.373 to 0.376)	0.731 (95% CI = 0.729 to 0.732)	0.561 (95% CI = 0.559 to 0.5
0.4	mde_ma1	dys_ma	man_ma3
0.1	0.395 (95% CI = 0.394 to 0.396)	0.763 (95% CI = 0.762 to 0.764)	0.595 (95% CI = 0.594 to 0.5
0.3	mde_ma1 $0.465 (0.5\% C) = 0.465 to 0.466)$	dys_ma	man_ma3
0.3	0.465(95% Cl = 0.465 to 0.466)	0.851 (95% CI = 0.85 to 0.851)	0.701(95% Cl = 0.701 to 0.7)
0.5	0.525 (95% Cl = 0.524 to 0.525)	0.908 (95% C) = 0.908 to 0.908)	0.787 (95% C) = 0.786 to 0.7
0.5	mde ma?	dvs ma	man ma3
0.7	0.568(95% Cl = 0.568 to 0.569)	0.946(95% Cl = 0.946 to 0.947)	$0.855(95\% \text{ Cl} = 0.854 \text{ to } 0.8555 \text{ (0.854 \text{ to } 0.854 to $
0.05	mde ma2	dvs ma	man ma3
0.05	0.688 (95% CI = 0.687 to 0.69)	0.909 (95% CI = 0.908 to 0.909)	0.831 (95% CI = 0.83 to 0.83
0.1	mde ma1	dys ma	man ma3
0.1	0.688 (95% CI = 0.687 to 0.689)	0.912 (95% CI = 0.911 to 0.913)	0.836 (95% CI = 0.835 to 0.8
0.3	mde_ma2	dys_ma	man_ma3
0.3	0.71 (95% Cl = 0.709 to 0.711)	0.93 (95% CI = 0.93 to 0.93)	0.862 (95% CI = 0.861 to 0.8
0.5	mde_ma2	dys_ma	man_ma3
0.5	0.729 (95% CI = 0.728 to 0.729)	0.944 (95% CI = 0.943 to 0.944)	0.882 (95% CI = 0.882 to 0.8
0.7	mde_ma1	dys_ma	man_ma3
0.7	0.745 (95% CI = 0.744 to 0.745)	0.954 (95% Cl = 0.954 to 0.955)	0.9 (95% CI = 0.9 to 0.9)
0.05	mde_ma1	dys_ma	man_ma3
0.05	0.828 (95% CI = 0.827 to 0.829)	0.958 (95% CI = 0.957 to 0.958)	0.918 (95% CI = 0.917 to 0.9
0.1	mde_ma2	dys_ma	man_ma3
0.1	0.838 (95% CI = 0.838 to 0.839)	0.301 (32% CI = 0.301 (0 0.301)	0.925 (95% Cl = 0.924 to 0.9929 man
0.3	0.856 (95% C) = 0.856 to 0.857	0.969 (95% C) = 0.968 to 0.969)	
0.5	mde ma2	dvs ma	man ma3
0.5	0.862 (95% Cl = 0.862 to 0.863)	0.972 (95% CI = 0.972 to 0.972)	0.942 (95% Cl = 0.942 to 0.942
0.7	mde ma2	dys ma	man ma3
0.7	0.865 (95% CI = 0.865 to 0.866)	0.974 (95% CI = 0.974 to 0.974)	0.946 (95% CI = 0.946 to 0.9
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	0.5 0.7 0.05 0.05 0.1 0.1 0.3 0.3 0.5 0.5 0.5 0.7 0.7 0.7 0.05 0.05 0.05	0.5 0.525 (95% CI = 0.524 to 0.525) 0.7 mde_ma2 0.7 0.568 (95% CI = 0.568 to 0.569) 0.05 mde_ma2 0.05 0.688 (95% CI = 0.687 to 0.69) 0.1 mde_ma1 0.1 0.688 (95% CI = 0.687 to 0.689) 0.3 mde_ma2 0.3 0.71 (95% CI = 0.709 to 0.711) 0.5 mde_ma2 0.5 0.729 (95% CI = 0.728 to 0.729) 0.7 mde_ma1 0.7 0.745 (95% CI = 0.744 to 0.745) 0.05 mde_ma1 0.05 0.828 (95% CI = 0.827 to 0.829) 0.1 mde_ma2 0.1 0.838 (95% CI = 0.838 to 0.839) 0.3 mde_ma2 0.3 0.856 (95% CI = 0.865 to 0.863) 0.7 mde_ma2 0.5 0.862 (95% CI = 0.865 to 0.866)	0.5 0.525 (95% CI = 0.524 to 0.525) 0.908 (95% CI = 0.908 to 0.908) 0.7 mde_ma2 dys_ma 0.7 0.568 (95% CI = 0.568 to 0.569) 0.946 (95% CI = 0.946 to 0.947) 0.05 mde_ma2 dys_ma 0.05 0.688 (95% CI = 0.687 to 0.69) 0.909 (95% CI = 0.908 to 0.909) 0.1 mde_ma1 dys_ma 0.1 0.688 (95% CI = 0.687 to 0.69) 0.912 (95% CI = 0.911 to 0.913) 0.3 mde_ma2 dys_ma 0.3 0.71 (95% CI = 0.709 to 0.711) 0.93 (95% CI = 0.93 to 0.93) 0.5 mde_ma2 dys_ma 0.5 0.729 (95% CI = 0.728 to 0.729) 0.944 (95% CI = 0.943 to 0.944) 0.7 mde_ma1 dys_ma 0.5 0.729 (95% CI = 0.724 to 0.745) 0.954 (95% CI = 0.954 to 0.955) 0.05 mde_ma1 dys_ma 0.7 0.745 (95% CI = 0.827 to 0.829) 0.958 (95% CI = 0.954 to 0.958) 0.1 mde_ma2 dys_ma 0.1 0.838 (95% CI = 0.838 to 0.839) 0.961 (95% CI = 0.961 to 0.961) 0.3 mde_ma2 dys_ma 0.3 0.856 (95% CI = 0.862 to 0.863) 0.972 (95% CI = 0

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Assu corr betv sym	imed elations veen input ptoms	Assumed prevalence of input symptoms	Major depressive episodes	Dysthymic disorder	Manic episodes
	0	0.05	mde_bias2	dys_bias	man_bias2
	0	0.05	0 (95% CI = 0 to 0)	0.028 (95% CI = 0.028 to 0.028)	0.001 (95% CI = 0.001 to 0.0
	0	0.1	mde_bias2	dys_bias	man_bias2
	0	0.1	0.004 (95% Cl = 0.004 to 0.004)	0.053 (95% Cl = 0.053 to 0.054)	0.011 (95% CI = 0.011 to 0.0
	0	0.3	mde_bias2	dys_bias	man_bias1
	0	0.3	0.015 (95% CI = 0.015 to 0.015)	0.045 (95% CI = 0.045 to 0.045)	0.089 (95% CI = 0.089 to 0.0
	0	0.5	mde_blas	dys_blas	man_bias1
	0	0.5	0.013 (95% CI = 0.013 to 0.014)	0.007 (95% CI = 0.007 to 0.007)	0.035 (95% CI = 0.034 to 0.0
	0	0.7	0.01 (95% C) = 0.01 to 0.01)	0 (95% C) = 0 to 0)	0.002 (95% Cl = 0.002 to 0.002
	01	0.05	mde hias2	dvs bias	man bias1
	0.1	0.05	0.037 (95% Cl = 0.037 to 0.037)	0.113(95% Cl = 0.113 to 0.114)	0.083(95% Cl = 0.083 to 0.03)
	0.1	0.1	mde bias2	dvs bias	man bias1
	0.1	0.1	0.047 (95% CI = 0.047 to 0.048)	0.122 (95% CI = 0.121 to 0.122)	0.116 (95% CI = 0.115 to 0.1
	0.1	0.3	mde_bias2	dys_mi_bias	man_bias1
	0.1	0.3	0.077 (95% CI = 0.077 to 0.077)	0.105 (95% Cl = 0.105 to 0.106)	0.198 (95% CI = 0.197 to 0.1
	0.1	0.5	mde_bias2	dys_mi_bias	man_bias1
	0.1	0.5	0.079 (95% CI = 0.079 to 0.08)	0.073 (95% CI = 0.073 to 0.073)	0.166 (95% CI = 0.166 to 0.1
	0.1	0.7	mde_bias2	dys_mi_bias	man_bias1
	0.1	0.7	0.065 (95% CI = 0.065 to 0.065)	0.047 (95% CI = 0.046 to 0.047)	0.094 (95% CI = 0.093 to 0.0
	0.4	0.05	mde_blas1 0.204 (05% Cl = 0.202 to 0.205)	dys_mi_bias	man_bias1 0.422/05% Cl = 0.421 to 0.4
	0.4	0.05	0.294 (95% CI = 0.293 (0 0.295) mde_bias1	0.415 (95% CI = 0.413 (0 0.410)	0.432 (95% CI = 0.431 (0 0.4)
	0.4	0.1	0.304 (95% Cl = 0.303 to 0.304)	0.419(95% C) = 0.418 to 0.42)	0.445(95% C) = 0.444 to 0.4
	0.4	0.3	mde bias1	dvs mi bias	man bias1
	0.4	0.3	0.335 (95% CI = 0.334 to 0.335)	0.411 (95% Cl = 0.411 to 0.412)	0.473 (95% CI = 0.472 to 0.4
	0.4	0.5	mde bias1	dys mi bias	man bias1
	0.4	0.5	0.354 (95% CI = 0.354 to 0.355)	0.395 (95% Cl = 0.395 to 0.396)	0.475 (95% CI = 0.474 to 0.4
	0.4	0.7	mde_bias1	dys_mi_bias	man_bias1
	0.4	0.7	0.356 (95% Cl = 0.355 to 0.356)	0.367 (95% Cl = 0.366 to 0.367)	0.451 (95% Cl = 0.45 to 0.45
	0.7	0.05	mde_bias1	dys_mi_bias	man_bias1
	0.7	0.05	0.616 (95% CI = 0.615 to 0.617)	0.705 (95% CI = 0.704 to 0.706)	0.723 (95% CI = 0.722 to 0.7
	0.7	0.1	mde_bias1		man_bias1
	0.7	0.1	0.011 (95% CI = 0.011 to 0.612)	dvs. mi. bias	0.72 (95% CI = 0.72 to 0.721)
	0.7	0.3	0.623 (95% CL = 0.623 to 0.624)	0.699 (95% Cl = 0.699 to 0.7)	0.728 (95% C) = 0.728 to 0.7
	0.7	0.5	mde bias1	dvs mi bias	man bias1
	0.7	0.5	0.632 (95% CI = 0.632 to 0.633)	0.696 (95% CI = 0.696 to 0.697)	0.731 (95% Cl = 0.731 to 0.7
	0.7	0.7	mde_bias1	dys_mi_bias	man_bias1
	0.7	0.7	0.639 (95% CI = 0.638 to 0.639)	0.693 (95% CI = 0.692 to 0.693)	0.732 (95% CI = 0.731 to 0.7
	0.9	0.05	mde_bias1	dys_mi_bias	man_bias1
	0.9	0.05	0.777 (95% CI = 0.776 to 0.778)	0.835 (95% CI = 0.834 to 0.835)	0.847 (95% CI = 0.847 to 0.8
	0.9	0.1	mde_bias1	dys_mi_bias	man_bias1
	0.9	0.1	0.788 (95% CI = 0.788 to 0.789)	0.842 (95% CI = 0.841 to 0.843)	0.855 (95% CI = 0.854 to 0.8
	0.9	0.3	mde_bias1	dys_mi_bias	man_bias1
	0.9	0.3	0.807 (95% CI = 0.806 to 0.807)	0.854 (95% CI = 0.853 to 0.854)	0.867 (95% CI = 0.867 to 0.8
	0.9	0.5	1100 = 00000000000000000000000000000000	uys_mi_{Dias}	man_{Dlas1}
	0.9	0.5	mde hiss1	dvs mi bias	0.07 (52% CI = 0.87 (0 0.871)
	0.9	0.7	$0.812 (95\% \text{ C}) = 0.811 \pm 0.812$	0.853 (95% C) = 0.852 + 0.952)	0.869 (95% CI = 0.860 + 0.9

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Assumed correlations between input	Assumed prevalence of input symptoms	Major depressive episodes	Dysthymic disorder	Manic episodes
symptoms	0.05	0.002 (05% CL 0.002 to 0.002)	0.122 (05% CL 0.121 += 0.122)	0.004 (05% CL 0.004 to 0.005)
0	0.05	0.003 (95% Cl = 0.002 to 0.003)	0.122 (95% Cl = 0.121 to 0.123)	0.004 (95% Cl = 0.004 to 0.005)
0	0.1	0.024 (95% Cl = 0.023 to 0.024)	0.305(95% Cl = 0.304 to 0.306)	0.039 (95% Cl = 0.038 to 0.039)
0	0.3	0.348(95%(1=0.348t0).349)	0.842 (95% CI = 0.841 to 0.842)	0.483 (95% Cl = 0.482 to 0.483)
0	0.5	0.849 (95% Cl = 0.849 to 0.849)	0.986 (95% Cl = 0.986 to 0.986)	0.817 (95% Cl = 0.817 to 0.817)
0	0.7	0.823 (95% Cl = 0.823 to 0.823)	1(95% C) = 1 to 1)	0.967 (95% Cl = 0.967 to 0.967)
0.1	0.05	0.143 (95% Cl = 0.141 to 0.144)	0.435 (95% Cl = 0.433 to 0.436)	0.212 (95% Cl = 0.211 to 0.213)
0.1	0.1	0.198(95% Cl = 0.197 to 0.199)	0.539(95% CI = 0.538 to 0.54)	0.29(95% Cl = 0.289 to 0.291)
0.1	0.3	0.45(95% Cl = 0.45 to 0.451)	0.826 (95% CI = 0.826 to 0.827)	0.588 (95% Cl = 0.588 to 0.589)
0.1	0.5	0.003 (95% Cl = 0.003 (0.004)	0.952 (95% CI = 0.952 (0 0.952)	0.799(95% Cl = 0.799(0.0.799)
0.1	0.7	0.809(95% Cl = 0.809(0.809)	0.391(95% Cl = 0.391(0.0.991)	0.922 (95% Cl = 0.922 (0.922)
0.4	0.03	0.387 (95% Cl = 0.385 to 0.388)	0.782(95% Cl = 0.781(0.783))	0.675(95% Cl = 0.674(0.070)
0.4	0.1	0.607 (95% Cl = 0.600 to 0.608)	0.807 (95% Cl = 0.807 (0.808)	0.058(95% Cl = 0.057(0.058))
0.4	0.5	0.088(95% Cl = 0.088(0.089)) 0.761(95% Cl = 0.761 to 0.762)	0.878(95% Cl = 0.877(00.878)	0.775(95% Cl = 0.774(0.0.775))
0.4	0.5	0.821 (95% Cl = 0.821 to 0.822)	0.956 (95% Cl = 0.956 to 0.956)	0.887 (95% Cl = 0.887 to 0.888)
0.7	0.05	0.813(95% Cl = 0.812 to 0.814)	0.925 (95% Cl = 0.925 to 0.926)	0.877 (95% Cl = 0.877 to 0.878)
0.7	0.03	0.826 (95% Cl = 0.826 to 0.827)	0.928 (95% Cl = 0.927 to 0.928)	0.881 (95% Cl = 0.881 to 0.882)
0.7	0.1	0.86 (95% Cl = 0.86 to 0.86)	0.923 (95% Cl = 0.927 to 0.923)	0.001(55% Cl = 0.001(6)(0.002)
0.7	0.5	0.88 (95% Cl = 0.88 to 0.88)	0.953 (95% Cl = 0.953 to 0.953)	0.913 (95% Cl = 0.913 to 0.913)
0.7	0.7	0.895 (95% Cl = 0.895 to 0.895)	0.962 (95% Cl = 0.962 to 0.962)	0.925 (95% Cl = 0.925 to 0.925)
0.9	0.05	0.903 (95% Cl = 0.903 to 0.904)	0.965 (95% Cl = 0.965 to 0.966)	0.941 (95% Cl = 0.94 to 0.941)
0.9	0.1	0.91 (95% CI = 0.91 to 0.911)	0.968 (95% CI = 0.968 to 0.968)	0.945 (95% CI = 0.945 to 0.945)
0.9	0.3	0.923 (95% CI = 0.923 to 0.923)	0.974 (95% CI = 0.974 to 0.974)	0.954 (95% CI = 0.953 to 0.954)
0.9	0.5	0.928 (95% CI = 0.928 to 0.928)	0.976 (95% CI = 0.976 to 0.977)	0.958 (95% CI = 0.957 to 0.958)
0.9	0.7	0.932 (95% Cl = 0.932 to 0.932)	0.978 (95% Cl = 0.978 to 0.978)	0.96 (95% Cl = 0.96 to 0.96)

Assumed correlations between input symptoms	Assumed prevalence of input symptoms	Major depressive episodes	Dysthymic disorder	Manic episodes
0	0.05	0.003 (95% CI = 0.002 to 0.003)	0.029 (95% CI = 0.029 to 0.03)	0.004 (95% CI = 0.004 to 0.004
0	0.1	0.013 (95% CI = 0.012 to 0.013)	0.056 (95% CI = 0.056 to 0.056)	0.017 (95% CI = 0.017 to 0.017
0	0.3	0.083 (95% CI = 0.083 to 0.083)	0.047 (95% CI = 0.047 to 0.047)	0.098 (95% CI = 0.098 to 0.099
0	0.5	0.111 (95% CI = 0.111 to 0.112)	0.007 (95% CI = 0.007 to 0.007)	0.039 (95% CI = 0.038 to 0.039
0	0.7	0.095 (95% CI = 0.095 to 0.095)	0 (95% CI = 0 to 0)	0.012 (95% CI = 0.012 to 0.013
0.1	0.05	0.083 (95% CI = 0.082 to 0.084)	0.145 (95% CI = 0.144 to 0.146)	0.126 (95% CI = 0.125 to 0.127
0.1	0.1	0.096 (95% CI = 0.095 to 0.097)	0.156 (95% Cl = 0.155 to 0.156)	0.154 (95% CI = 0.153 to 0.154
0.1	0.3	0.145 (95% CI = 0.144 to 0.145)	0.139 (95% CI = 0.138 to 0.139)	0.216 (95% CI = 0.216 to 0.216
0.1	0.5	0.172 (95% CI = 0.172 to 0.173)	0.097 (95% CI = 0.097 to 0.097)	0.182 (95% CI = 0.181 to 0.182
0.1	0.7	0.175 (95% CI = 0.175 to 0.175)	0.065 (95% CI = 0.064 to 0.065)	0.115 (95% CI = 0.115 to 0.116
0.4	0.05	0.421 (95% CI = 0.419 to 0.423)	0.455 (95% CI = 0.453 to 0.456)	0.505 (95% CI = 0.504 to 0.506
0.4	0.1	0.422 (95% CI = 0.421 to 0.423)	0.454 (95% CI = 0.453 to 0.455)	0.507 (95% CI = 0.506 to 0.508
0.4	0.3	0.435 (95% CI = 0.434 to 0.435)	0.442 (95% CI = 0.442 to 0.443)	0.512 (95% CI = 0.512 to 0.513
0.4	0.5	0.452 (95% CI = 0.452 to 0.453)	0.427 (95% CI = 0.427 to 0.427)	0.506 (95% CI = 0.505 to 0.506
0.4	0.7	0.46 (95% Cl = 0.459 to 0.46)	0.403 (95% CI = 0.402 to 0.403)	0.481 (95% CI = 0.481 to 0.482
0.7	0.05	0.728 (95% CI = 0.727 to 0.729)	0.729 (95% CI = 0.728 to 0.731)	0.764 (95% CI = 0.763 to 0.765
0.7	0.1	0.722 (95% CI = 0.721 to 0.723)	0.723 (95% CI = 0.722 to 0.724)	0.76 (95% CI = 0.759 to 0.761)
0.7	0.3	0.726 (95% Cl = 0.726 to 0.727)	0.722 (95% CI = 0.722 to 0.723)	0.761 (95% CI = 0.761 to 0.762
0.7	0.5	0.732 (95% CI = 0.731 to 0.732)	0.72 (95% CI = 0.719 to 0.72)	0.76 (95% CI = 0.76 to 0.761)
0.7	0.7	0.737 (95% CI = 0.736 to 0.737)	0.717 (95% CI = 0.716 to 0.717)	0.758 (95% CI = 0.758 to 0.759
0.9	0.05	0.852 (95% CI = 0.851 to 0.853)	0.85 (95% CI = 0.849 to 0.851)	0.871 (95% CI = 0.871 to 0.872
0.9	0.1	0.86 (95% CI = 0.859 to 0.861)	0.857 (95% CI = 0.856 to 0.857)	0.876 (95% CI = 0.876 to 0.872
0.9	0.3	0.872 (95% CI = 0.871 to 0.872)	0.867 (95% CI = 0.867 to 0.868)	0.886 (95% CI = 0.886 to 0.886
0.9	0.5	0.874 (95% CI = 0.874 to 0.875)	0.869 (95% CI = 0.868 to 0.869)	0.888 (95% CI = 0.887 to 0.888
0.9	0.7	0.874 (95% CI = 0.874 to 0.875)	0.867 (95% CI = 0.866 to 0.867)	0.886 (95% CI = 0.886 to 0.886

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4	559 560	Figure 1. The assumed and derived prevalence rates for major depressive episodes, dysthymic disorder, and manic
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/ 8	562	Note: each of the combinations of assumed provalence rates and between variable correlations of
9	562	the input symptoms for major depressive episodes, dysthymic disorder, and manic episodes was
10	505	represented by one circle, but the circles overlapped in the graph
11	504	represented by one circle, but the circles overlapped in the graph.
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1 2		
3 4 5	567 568	Figure 2. The prevalence rates of an intermediate variable for the diagnosis of major depressive episodes.
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$ 5 \\ 6 \\ 7 \\ 8 \\ 9 \\ 10 \\ 11 \\ 12 \\ 13 \\ 14 \\ 15 \\ 17 \\ 18 \\ 19 \\ 20 \\ 22 \\ 24 \\ 25 \\ 26 \\ 27 \\ 28 \\ 29 \\ 30 \\ 1 \\ 32 \\ 33 \\ 34 \\ 35 \\ 36 \\ 37 \\ 38 \\ 90 \\ 41 \\ 42 \\ 44 \\ 45 \\ 46 \\ 47 \\ 48 \\ 9 \\ 51 \\ 52 \\ 54 \\ 55 \\ 57 $	569 570 571 573 574 575	Note: The intermediate variable is "significant unintentional weight loss or gain" and the input symptoms are "significant unintentional weight loss" and "significant unintentional weight gain". The black line represents the situation where the prevalence rates of the input symptoms are the same as that of the intermediate variable. Lines above the black lines have prevalence rates larger than those of the input symptoms.
59 60		

3 4	577	Figure 3. The prevalence rates of dysthymic disorder.
5	578	
6 7		
8	579	Note: Dysthymic disorder is diagnosed when both the major (depressed mood most of the day for
9 10	580	more days than not, for at least 2 years) and minor criteria (at least two of the six items) are
10	581	confirmed. The black line represents the situation where the prevalence rates of the input
12	582	symptoms are the same as those of the intermediate variable. Lines below the black lines have
13	583	prevalence rates lower than those of the input symptoms.
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 3 587 Figure 4. The prevalence rates of major depressive episodes. 	
4	
5 588 6	
7 589 Note: Major depressive episodes are diagnosed when both major and minor criteria ar	e confirmed.
$\frac{8}{9}$ 590 The black line represents the situation where the prevalence rates of the input sympto	ms are the
10 591 same as that of the intermediate variable. Lines below the black lines have prevalence	rates lower
11 592 than those of the input symptoms.	
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2 3	гос	
4	590	Figure 5. The prevalence rates of manic episodes
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6 7	F00	Note: Mania anisodos que discusso du uban the summtance present es described in the discussorie
8	590	monul. The black line represents the situation where the prevalence rates of the input symptoms
9	599	are the same as those of the input symptoms. Lines below the black lines have prevalence rates
10 11	601	lower than those of the input symptoms. Lines below the black lines have prevalence rates
12	001	lower than those of the input symptoms.
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1 2 3	605	Figure 6. The approximation of the diagnosis of dysthymic disorder by the input symptoms, the bias variables, and both,
4 5	606	measured by R-squared
6 7	607	
8	608	Note: the diagnosis of dysthymic disorder is approximated by the input symptoms, the bias
10	609 610	determined by adjusted R-squared. See Table 4 for the details in the input symptoms and the bias
11 12	611 612	variables. The assumed correlations between the input symptoms are 0.4 and the assumed
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3	616	Supplemental materials
5	617	S 1. Characteristics of the input symptoms for simulations
6 7	618	S 2. R codes to be used with S1 to simulate populations
8 9	619	S 3. Correlations between the symptoms
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Numbers of variables

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12	4	dysthymia, and manic episodes
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15	5	Yi-Sheng Chao ^{1*} , Kuan-Fu Lin, ² Chao-Jung Wu ³ , Hsing-Chien Wu ⁴ , Hui-Ting
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24	12	Ming University Hospital, Yilan 260 Taiwan, "Department of Chest Medicine,
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Page	42	of	83

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```
title: "2019_09_06 simulated mental illnesses"
          author: "Yi-Sheng Chao"
          date: "November 22, 2018"
          output: pdf_document
          editor_options:
             chunk_output_type: inline
10
11
12
13
          ##Adding correlations to the random variables
14
15
           ```{r}
16
 library(bindata)
17
18
 library(openxlsx)
19
 resu = read.xlsx("A simulation study to demonstrate the biases in three
20
 diagnoses of mental illnesses.xlsx", sheet = "Prob 1")
21
 names(resu)
22
 unique(resu$variable)
23
 memory.limit(size = 10^13)
24
 ssize = 10^{5}
25
 times = 10^2
26
27
 prevalence = c(0.05, 0.1, 0.3, 0.5, 0.7)
28
 rho = c(0, 0.1, 0.4, 0.7, 0.9)#correlation coefficients of the input
29
 symptoms
30
31
 collect = c("mean", "max",
32
 "min", "derivedprevalence", "coef", "coefse", "p", "intercept",
 "interceptp", "r2", "subcoef", "subcoefse", "subp", "subintercept",
33
34
 "subinterceptp","subr2", "appbyownr2", //appbybiasr2", "appbyallr2",
35
 "appbyownvar", "appbybiasvar", "appbyallvar", "appbyownn", "appbybiasn",
36
 "appbyalln")
37
38
39
 set.seed(1)
40
41
42
 ##Create a simulated data set to extract variables
43
 for(preval in 1:length(prevalence)){
44
 for(rh in 1:length(rho)){
45
46
47
 library(openxlsx)
48
 resu = read.xlsx("A simulation study to demonstrate the biases in three
49
 diagnoses of mental illnesses.xlsx", sheet = "Prob 1")
50
51
 # foreach(c = 1:times) %dopar% {
52
 for(c in 1:times){
53
54
 library(bindata)
55
 bindata = as.data.frame(rmvbin(ssize, rep(prevalence[preval], 40),
56
 bincorr=(1 - rho[rh])*diag(40) + rho[rh]))
57
 bindata2 = as.data.frame(rmvbin(ssize, rep(prevalence[preval], 20),
58
 bincorr=(1 - rho[rh])*diag(20) + rho[rh]))
59
60
 ##demographic characteristics
```

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```
sim = data.frame(1:ssize)
names(sim) = "id"
sim$female = rbinom(n = ssize, size = 1, prob = 0.51)
sim$age = sample(30:60, ssize, replace = TRUE)
sim$edu = rnorm(ssize, mean = 12, sd = 5)
sim edu[which(sim edu <= 0)] = 0
sim$id = NULL
sim$mde_ma1 = bindata[,1]
sim$mde_ma2 = bindata[,2]
sim$mde_mi3_1 = bindata[,3]
sim$mde_mi3_2 = bindata[,4]
sim$mde_mi3 = 1*((sim$mde_mi3_1 + sim$mde_mi3_2) > 0)
sim$mde_mi3_bias = sim$mde_mi3 - sim$mde_mi3_1 - sim$mde_mi3_2
sim$mde mi4 1 = bindata[,5]
sim$mde mi4 2 = bindata[,6]
sim$mde_mi4 = 1*((sim$mde_mi4_1 + sim$mde_mi4_2) > 0)
sim$mde_mi4_bias = sim$mde_mi4 - sim$mde_mi4_1 - sim$mde_mi4_2
sim$mde_mi5_1 = bindata[,7]
sim$mde_mi5_2 = bindata[,8]
sim$mde_mi5 = 1*((sim$mde_mi5_1 + sim$mde_mi5_2) > 0)
sim$mde_mi5_bias = sim$mde_mi5 - sim$mde_mi5_1 - sim$mde_mi5_2
sim$mde_mi6_1 = bindata[,9]
sim$mde_mi6_2 = bindata[,10]
sim$mde_mi6 = 1*((sim$mde_mi6_1 + sim$mde_mi6_2) > 0)
sim$mde_mi6_bias = sim$mde_mi6 - sim$mde_mi6_1 - sim$mde_mi6_2
sim$mde_mi7_1 = bindata[,11]
sim mde mi7 2 = bindata[,12]
sim$mde_mi7 = 1*((sim$mde_mi7_1 + sim$mde_mi7_2) > 0)
sim$mde mi7 bias = sim$mde mi7 - sim$mde mi7 1 - sim$mde mi7 2
sim$mde mi8 1 = bindata[,13]
sim$mde_mi8_2 = bindata[,14]
sim$mde_mi8 = 1*((sim$mde_mi8_1 + sim$mde_mi8_2) > 0)
sim$mde_mi8_bias = sim$mde_mi8 - sim$mde_mi8_1 - sim$mde_mi8_2
sim$mde_mi9 = bindata[,15]
sim$mde_bias1 = 1 * ((sim$mde_mi3 + sim$mde_mi4 + sim$mde_mi5 +
sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9)>2) - (sim$mde_mi3
+ sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 +
sim$mde mi9)
sim$mde bias2 = 1 * ((sim$mde mi3 + sim$mde mi4 + sim$mde mi5 +
sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9)>3) - (sim$mde_mi3
+ sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 +
sim$mde_mi9)
sim$mde = sim$mde_ma1 * sim$mde_ma2 * (sim$mde_mi3 + sim$mde_mi4 +
sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9 +
sim$mde_bias1) + (1- sim$mde_ma1 * sim$mde_ma2) * (sim$mde_ma1 *
sim$mde_ma2) * (sim$mde_mi3 + sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 +
sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9 + sim$mde_bias2)
```









































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### A simulation study to demonstrate biases created by diagnostic criteria of mental illnesses: major depressive episodes, dysthymia, and manic episodes

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Secondary Subject Heading:	Epidemiology, Research methods, Diagnostics
Keywords:	MENTAL HEALTH, Depression & mood disorders < PSYCHIATRY, EPIDEMIOLOGY, STATISTICS & RESEARCH METHODS
	·

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# A simulation study to demonstrate biases created by diagnostic criteria of mental illnesses: major depressive episodes, dysthymia, and manic episodes

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### 28 Abstract

### **Objectives**

Composite diagnostic criteria alone are likely to create and introduce biases into diagnoses
 that subsequently have poor relationships with input symptoms. This study aims to
 understand the magnitudes of biases created by diagnostic criteria alone and introduced into
 the diagnoses of mental illnesses with large disease burdens (major depressive episodes,

- 11 33 the diagnoses of mental linesses with large disease burdens (major depressive episodes, 12 34 dysthymic disorder, and manic episodes) and the relationships between the diagnoses and
- <sup>13</sup> 35 the input symptoms.

### <sup>15</sup> 36 **Settings**

<sup>16</sup> 17 37 General psychiatric care.

### 19 38 **Participants**

Without real-world data available to the public, 100,000 subjects were simulated and the input symptoms were assigned based on the assumed prevalence rates (0.05, 0.1, 0.3, 0.5, and 0.7) and correlations between symptoms (0, 0.1, 0.4, 0.7, and 0.9). The input symptoms were extracted from the diagnostic criteria. The diagnostic criteria were transformed into mathematical equations to demonstrate the sources of biases and convert the input symptoms into diagnoses.

# 28<br/>2945Primary and secondary outcomes

 $_{30}^{29}$  46 Biases due to data censoring or categorization introduced into the intermediate variables,

- 47 and the three diagnoses were measured. The relationships between the input symptoms
- 48 and diagnoses were interpreted using forward stepwise linear regressions.
   33

### 49 Results

The prevalence rates of the diagnoses were lower than those of the input symptoms and proportional to the assumed prevalence rates and the correlations between the input symptoms. Certain input or bias variables consistently explained the diagnoses better than the others. Except for zero correlations and 0.7 prevalence rates of the input symptoms for the diagnosis of dysthymic disorder, the input symptoms could not fully explain the diagnoses.

42 55 ulagnoses. 

### 56 Conclusions

57 There are biases created due to composite diagnostic criteria and introduced into the
58 diagnoses. The design of the diagnostic criteria determines the prevalence of the diagnoses,
59 the relationships between the input symptoms, the diagnoses, and the biases. The
60 importance of the input symptoms has been distorted largely by the diagnostic criteria.

- 51 61 Trial registration
  - 62 Not applicable

# 54 63 Strength and limitation

- The prevalence of three mental illnesses was determined by the prevalence of the
   input symptoms and modified by the diagnostic criteria and correlations between the
   input variables in simulated populations.

- Biases due to data censoring or categorization were created by the diagnostic criteria
  and introduced into the intermediate variables and the three diagnoses of mental
  illnesses in simulated populations.
  The diagnostic criteria modified the importance of the input symptoms: certain input
  - 3. The diagnostic criteria modified the importance of the input symptoms; certain input symptoms or bias variables were weighted more than expected in simulated populations.
  - 4. The design of diagnostic criteria influenced the diagnosis prevalence. With the same input symptom prevalence, dysthymic disorder was the most prevalent among three illnesses. Major depressive episodes were the least prevalent.
  - 5. This study is based on simulated data and needs to be verified with real-world data. to peer leview only

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### 78 Background

The diagnoses of several mental illnesses in patients are often made based on a variety of criteria. These criteria often involve symptoms reported by the patients.[1, 2] For example, the diagnosis of major depressive disorder defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) requires at least one major depressive episode.[1, 2] For each major depressive episode, the major criteria are "depressive mood and/or loss of interest or pleasure in life activities for at least 2 weeks".[1, 2] In addition to the major criteria, the patients need to report at least five of the nine symptoms that "cause clinically significant impairment in social, work, or other important areas of functioning almost every day," including insomnia or hypersomnia and fatigue or loss of interest.[1, 2] In other words, patients need to match both the major and minor criteria before being diagnosed with a major depressive episode.

Historically this symptom-based diagnostic approach developed by Feighner et al. has been widely accepted. [3, 4] Since then, mental illnesses can be diagnosed through different sets of criteria. This approach is important because clinicians become capable of screening important symptoms before diagnosing and treating patients accordingly. In fact, these criteria can also be seen as composite measures that use multiple measures to capture disorders that may not be quantified with single variables.[5, 6] Recent studies on composite measures have found them problematic because biases can be introduced while aggregating information from input variables.[6] The biases emerge while the sums of input variables are censored or while input variables are transformed inadequately.[6, 7] In other words, biases can be created when there is information in the composite measures that is not explained by and unrelated to the input variables.[6] For example, categorizing continuous variables considers individuals in the same group the same and disregards the heterogeneity between those in the same categories.[6] Such practices induce biases and decrease measurement precision.[6, 7] 

Currently there is no extensive review on the existence of these biases created by composite measures or medical diagnoses, and only selected diagnoses have been studied for such biases. These biases have been proven vital to another symptom-based composite measure, the diagnosis of frailty, a condition that often occurs in the elderly and is significantly associated with health outcomes, such as mortality, falls, and morbidity.[6] Frailty is diagnosed based on several symptoms and characterized by weakness and vulnerability to adverse health events.[6] While using one of the most widely used diagnostic criteria, the Biological Syndrome Model scores, to diagnose frailty,[8] biases alone can explain more than 71% of the variances of the frailty diagnosis.[6] The biases introduced by data censoring and data categorization can better explain the frailty diagnosis than the input symptoms.[6] 

Mostly designed as symptom-based composite measures, it is possible that the diagnostic criteria of mental illnesses also create and introduce biases into diagnoses so that the diagnoses could not be fully explained by the input symptoms. In concern of the biases created by the diagnostic criteria alone, this study aims first to understand the relationships between mental symptoms and diagnoses and then to quantify the potential role of the biases regarding the diagnoses by simulating populations with different prevalence rates and between-variable correlations of mental symptoms. 

### 122 Methods

### 123 Assumptions and simulation parameters

A file containing R codes to reproduce the simulations was attached in the supplementary file. Simulated populations with mental symptoms of different prevalence rates and between-variable correlations were created to interpret the diagnoses and understand the potential magnitudes of biases that could be introduced via data processing implied by the diagnostic criteria (reproducible using R codes and data in the supplementary file). Three diagnoses of mental illnesses were chosen for the leading associated disease burdens:[2] major depressive episodes for the diagnosis of major depressive disorder, dysthymic disorder, and manic episodes for the diagnosis of bipolar disorder.[1] 

There were assumptions made to simulate the populations (Table 1). First, for each simulation, the prevalence rates of the input symptoms were assumed to be similar for the three diagnoses in this study. Second, the input symptoms for the diagnoses of major depressive episodes and dysthymic disorder correlated with the same correlation coefficients.[9] The symptoms for the diagnosis of manic episodes correlated to one another. Third, the input symptoms for the diagnosis of manic episodes were created independently of those for the diagnosis of the other two mental illnesses. The assumptions of the prevalence rates and between-variable correlations were made because there was no acceptable-guality data on the symptoms of mental illnesses published. There were studies on the prevalence of mental illnesses, [10, 11] but the information on the prevalence of mental symptoms was very limited. There were variables about depression or anxiety collected in national surveys, such as the items collected through the Center for Epidemiologic Studies Depression Scale.[6, 12-18] However, these variables were not the symptoms used in the DSM-IV-TR. Lastly, we assumed that the diagnoses were made accurately based on the input symptoms reported precisely by patients. The diagnostic criteria in the DSM-IV-TR were strictly followed. However, these assumptions did not hold in the real world.[19] For simplicity and practicality reasons, we assumed perfect diagnostic guality by physicians and accurate reporting of the input symptoms by patients in the simulated populations. 

### 42 151 Diagnostic criteria as mathematical functions

The input symptoms were extracted from the major and minor criteria of the diagnoses and listed in Table 2 to Table 4. The input symptoms, major and minor criteria, and the diagnoses were assigned variable names. All input symptoms, items or domains in the major or minor criteria, and the diagnoses were binomial variables, presenting zero and one for the absence and presence of the symptoms, criteria, and the diagnoses respectively. For example, "insomnia" and "hypersomnia" were extracted from one of the minor criteria for the diagnosis of major depressive episodes.[1] "More talkative than usual" and "pressure to keep talking" were extracted from one of the minor criteria for the diagnosis of manic episodes.[1] 

Mathematical functions were generated based on the diagnostic criteria to convert input symptoms into diagnoses. For example, one of the minor criteria of dysthymic disorder was "poor appetite or overeating." This required two input symptoms and one bias variable to generate the criterion.[6] In other words, "poor appetite or overeating" equaling the sum of two input variables, "poor appetite" and "overeating," and a bias variable to achieve censoring of the sum of both variables.[6] The sum of two binomial variables could be zero, 

one and two for the subjects. However, to derive a binomial variable (having at least one symptom) based on a distribution of 0 to 2, the bias variable had values of -1 for subjects with both symptoms to obtain values less than or equal to one in all subjects.[6] Therefore, the bias variable had values of -1 for the subject with both symptoms and 0 for the other subjects. In addition to adding variables together to derive an intermediate variable or a diagnosis, multiplication, categorization, and other more complicated methods were used in the diagnostic criteria to generate diagnosis variables and domain variables in the major or minor criteria. 

For example, the diagnosis of dysthymic disorder required the confirmation of both the major criteria, "depressed mood most of the day for more days than not, for at least 2 years" and the minor criteria, "the presence of two or more of the following symptoms," at the same time.[1] The diagnosis based on whether subjects meeting both the major and minor criteria of dysthymic disorder is the same as identifying those with a multiplicative product of 1 of two binomial variables (0 and 1 for absence and presence of the major or minor criteria). In the equations, two binomial variables were multiplied to obtain the diagnosis of dysthymic disorder among those with a multiplicative product of 1. I2ndividuals could be assigned zero or one for whether they met both criteria, while the sum of major and minor criteria were zero, one or two for the individuals. Linearly, a bias variable with values of -1 or zero was created and those meeting the major or minor criteria were assigned -1.[6] For categorization of continuous variables, bias variables were required to remove the variations between the subjects in the same categories.[6] Other equations to generate the intermediate variables and the diagnoses were listed and explained in Table 2 to Table 4. 

**Generation of bias variables** 

Bias variables could be generated while binomial input symptoms were summed or multiplied to obtain binomial intermediate or diagnosis variables (see the example in the previous two paragraphs).[6] A visual presentation of how bias variables were generated was published.[6] Therefore the number of bias variables depended on the complexity of how the diagnoses were made. For example, six of the nine items or domains in the minor criteria for the diagnosis of major depressive episodes were the censored sums of the input symptoms and six bias variables were derived along with the intermediate variables that represented the items in the minor criteria. The other bias variables were described in Table 2 to Table 4. 

### Simulation parameters and simulated populations

We simulated populations of 100,000 subjects. There were five prevalence rates to simulate the input symptoms for the diagnosis of major depressive episodes, dysthymic disorder, and manic episodes: 0.05, 0.1, 0.3, 0.5, and 0.7. The correlations between the input symptoms were hypothesized to be 0, 0.1, 0.4, 0.7, and 0.9. There were 25 combinations of the assumed prevalence rates and between-variable correlations. The presence of the input symptoms was randomly assigned to the subjects after specifying the prevalence rates and between-variable correlations between the input symptoms.[20, 21] The intermediate and diagnosis variables were derived according to the equations in Table 2 to Table 4. For each combination of prevalence rates and between-variable correlations, the populations were simulated for 100 times to obtain the mean values and 95% confidence intervals (CIs) of derived prevalence rates, as well as the adjusted R squared and p values to approximate the diagnosis variables. 

Due to the existence of the biases, the input symptoms were not likely to fully explain

the diagnoses.[6] Therefore, the diagnoses were approximated by the input, bias, and

the diagnoses by the input symptoms and bias variables was assessed via adjusted R

suggested that the input symptoms perfectly explained the diagnosis.[14, 15, 23-26]

square: zero suggested that the input symptoms were unrelated to the diagnosis, and one

intermediate variables individually and collectively.[6, 12, 14, 16] The approximation was

conducted using forward-stepwise linear regressions.[6, 12, 14, 16, 22] The interpretability of

All statistical analyses were conducted within the R environment (v3.4.1)[27] and

 **Diagnosis approximation** 

RStudio (v1.0.153).[28] Two-tailed P values less than 0.05 were considered statistical significant. Patient and Public Involvement This is a simulation study that did not involve patients or human subjects. **Results** The derived prevalence rates of the input symptoms for the three mental illnesses matched the assumed rates in the supplementary file. The derived correlations between the input symptoms were close to assumed levels in the supplementary file. The simulations were successful and accurate based on the assumed prevalence rates and correlations. Prevalence of intermediate variables The items in the major and minor criteria were the intermediate variables necessary to create the diagnoses. The methods used to generate the intermediate variables were important for the prevalence rates of the intermediate variables and the derived diagnoses in Figure 1. For example, an intermediate variable, "significant unintentional weight loss or gain," was created by summing and censoring two binomial variables with values of zero and one (significant unintentional weight loss; significant unintentional weight gain). The prevalence rates of the intermediate variables were larger than those of the two input symptoms regardless of the assumed prevalence rates or between-variable correlations of the input symptoms. In contrast, the diagnosis of dysthymic disorder was a multiplication product of two intermediate binomial variables, the major and minor criteria, and the prevalence rates of dysthymic disorder were lower than those of the major or minor criteria under all combinations of assumed correlations and prevalence rates in Figure 2. Prevalence of mental illnesses The derived prevalence rates of three diagnoses were plotted against the assumed prevalence rates and correlations of the input symptoms in Figure 2 to Figure 4 and listed in Table 5. None of the three diagnoses had prevalence rates exceeding those of the input symptoms. In general, higher prevalence rates or between-variable correlations of the input symptoms were associated with higher prevalence rates in the three diagnoses, except for manic episodes that had higher prevalence rates (0.692) assuming zero correlations and 0.7 prevalence rates than the prevalence rate (0.679) assuming 0.1 correlations and 0.7 prevalence rates of the input symptoms. When compared across Figure 2 to Figure 4, given the same assumed prevalence rates and between-variable correlations of the input

symptoms, the diagnostic criteria of dysthymic disorder consistently generated diagnoses of
 the highest prevalence rates and the criteria of major depressive episodes created
 diagnoses of the least prevalence rates (see Table 5 for details).

# Associations between the diagnoses and individual input symptoms or 257 bias variables

The diagnoses were first interpreted with the input symptoms (including intermediate variables) and the bias variables individually. The diagnosis of dysthymic disorder, for example, was interpreted with the input symptoms, the bias variables, and both in Figure 5. For each simulation, the diagnosis of dysthymic disorder was approximated with an increasing number of the input symptoms, the bias variables, or both. After selecting the variables that best approximated the diagnosis based on adjusted R-squared, the input symptoms could explain a proportion of 0.955 of the diagnosis variance and the bias variables could explain at most a proportion of 0.405 of the diagnosis variance in Figure 5. With all variables used in the regression, the diagnosis could be perfectly explained by the input symptoms and bias variables (adjusted R-squared = 1). The individual input symptoms and the bias variables that individually best explained the diagnoses are listed in Table 6 and Table 7, respectively. 

For the diagnosis of major depressive episodes, the first and second items in the major criteria (variable names: mde ma1 for or mde ma2 in Table 2) individually best explained the diagnosis depending on the assumed prevalence rates and correlations in Table 6. For the diagnosis of dysthymic disorder, the major criteria (dys ma in Table 3) consistently and individually explained the diagnosis the best. For the diagnosis of manic episodes, the third item of the major criteria (man ma3 in Table 4) individually best explained the diagnosis in all combinations of assumed prevalence rates and correlations. However, the proportions of diagnosis variances best explained by individual input symptoms varied widely between 0.001 to 0.974, depending on the assumed prevalence rates and between-variable correlations. Based on the adjusted R-squared for individual input symptoms, certain input variables were more important than other symptoms due to a high correlation with the diagnoses, such as the major criteria for the diagnosis of dysthymic disorder. The prevalence rates and between-variable correlations were important to determine the relationships between input symptoms and diagnoses. 

Similarly, there were bias variables that consistently best explained the diagnoses in Table 7. For the diagnosis of major depressive episodes, the biases due to categorization of the numbers of confirmed input symptoms (mde\_bias1 and mde\_bias2 in Table 2) were the leading bias variable. The diagnosis of major depressive episodes not explained by the input symptoms or information censoring (mde bias in Table 2) was the leading bias variable in two combinations of the assumed prevalence rates and correlations. For the diagnosis of dysthymic disorder, the residual of the diagnosis not explained by the major and minor criteria (dys bias in Table 3) and the bias due to the categorization of the confirmed input symptoms in the minor criteria (dys mi bias) were the leading bias variables. For the diagnosis of manic episodes, the bias due to the categorization of the number of confirmed input symptoms in the minor criteria up to three (man bias1 in Table 4) was the leading bias variables, except for two combinations of the assumed prevalence rates and correlations, in which the bias due to categorization of the confirmed input symptoms in the minor criteria up to four (man bias2 in Table 4) best explained the diagnosis. However, the proportions of 

diagnosis variances explained by individual bias variables varied widely from zero to 0.87. Depending on the assumed prevalence rates and between-variable correlations of the input symptoms, certain bias variables were more important than other bias variables and even some input variables. The assumed prevalence rates and between-variable correlations were important factors for the relationships between the bias variables and the diagnoses. 

In general, the proportions of the diagnosis variance that could be explained by either individual input symptoms or single bias variables were low when the prevalence rates and between-variable correlations of the input symptoms were assumed to be low. With higher assumed prevalence rates or correlations, the proportions of the diagnoses explained by the single input symptoms or bias variables were higher. Across three diagnoses, the diagnosis of dysthymic disorder could be better explained by single input variables (higher adjusted R-squared), and the diagnosis of major depressive episodes was associated with the least adjusted R-squared. The bias variables of the diagnosis of manic episodes could explain the diagnosis individually better than the bias variables of the other two diagnoses. 

### 22 312 Approximating the diagnoses with input symptoms

When the diagnoses were approximated by their own input symptoms (Table 8), there were always some diagnosis variances that could not be explained by the input symptoms. In other words, the input symptoms could not fully explain the diagnoses, except for the diagnosis of dysthymic disorder that could be fully explained by the input symptoms (adjusted R-squared = 1) assuming zero between-variable correlations and 0.7 prevalence rates for the input symptoms. In Table 8, the proportions of diagnosis variances explained by input symptoms increased with higher assumed prevalence rates or between-variable correlations of the input symptoms in general. The input symptoms of dysthymic disorder explained the diagnosis better than those of the other two diagnoses under all combinations of assumed prevalence rates and between-variable correlations. However, the proportion of diagnosis variance explained by own input symptoms varied widely from 0.003 to 1.0. The assumed prevalence rates and between-variable correlations of the input symptoms and the design of the diagnostic criteria were all important for the relationships between input symptoms and diagnoses. 

# 41 327 Approximating the diagnoses with bias variables

The diagnoses were approximated with the bias variables of their own. The bias variables always explained some of the diagnosis variances, except for the diagnosis of dysthymic disorder assuming zero between-variable correlations and 0.7 prevalence rates for the input symptoms (adjusted R-squared = 0). With increasing assumed between-variable correlations for the input symptoms, the adjusted R-squared increased. However, given the same assumed between-variable correlations, the proportions of diagnosis variances explained by the bias variables might increase or decrease with the assumed prevalence rates. Compared to the adjusted R-squared in Table 8, the proportion of the diagnosis variances explained by the bias variables was always smaller than that explained by the input symptoms in Table 9. However, the proportions of the diagnosis variance explained by bias variables also varied widely from zero to 0.89. The assumed prevalence rates and between-variable correlations of input symptoms and the design of the diagnostic criteria were important for the relationship between the bias variables and the diagnoses. Only when the input symptoms for the diagnosis of dysthymic disorder were randomly and 

 independently prevalent to 70% of the simulated populations, the bias variables becameirrelevant to the diagnosis.

### **Discussion**

This study is a first attempt to assess the biases created by mental illness diagnostic criteria, as well as understand the relationships between input symptoms and the diagnoses of three mental illnesses: major depressive episodes (at least one episode required for the diagnosis of major depressive disorder), dysthymic disorder, and manic episodes. The diagnostic criteria of these three mental illnesses have been reviewed and rewritten as mathematical functions. Simulated populations of 100,000 for each of 100 simulations, with input symptoms of the three diagnoses, were created. For simplicity and practicality, the presence of the input symptoms was randomly assigned, and the input symptoms were assumed to have uniform prevalence rates and between-variable correlations. There were 25 combinations of assumed prevalence rates and between-variable correlations simulated. 

Mathematically, the diagnostic criteria are functions and composite measures to transform information from the input symptoms to diagnoses. There are bias variables created by the diagnostic criteria due to data processing.[6] There are three major mechanisms of introducing biases: censoring, data categorization,[7] and multiplication of input symptoms.[6] These mechanisms introduce information or biases that cannot be fully explained by the input symptoms.[6] The introduced biases can sometimes explain more than half of the variance in the diagnoses depending on the prevalence rates and between-variable correlations of the input symptoms. The findings show that the design of the diagnostic criteria is important for bias introduction and significant for the prevalence of the diagnoses in populations, the relationships between the input symptoms and the diagnoses, and the relationships between the bias variables and the diagnoses. 

### 366 The role of the diagnostic criteria

With the same assumptions in the prevalence rates and between-variable correlations of the input symptoms, the design of the diagnostic criteria of three mental illnesses can be compared to each other. The design of diagnostic criteria transform input symptoms into various diagnosis prevalence rates with implicit upper limits (i.e. no more prevalent than the input symptoms), unacknowledged differential weights on the input symptoms (i.e., certain input symptoms better explaining the diagnoses), and the introduction of biases (i.e., due to censoring, data categorization, or multiplication).

We were the first to notice that the prevalence rates of the three diagnoses were lower than those of the input symptoms if randomly distributed with uniform prevalence rates and correlations. Given similar assumed input symptom prevalence and correlations, dysthymic disorder is the most prevalent, and major depressive episodes are the least. The diagnosis of dysthymic disorder can be better explained by its input symptoms individually or collectively than the other two diagnoses. The diagnosis of major depressive episodes is least explained by own input symptoms individually or collectively. As expected, the diagnosis of the three mental illness is similar to composite measures or indices and is subject to the biases introduced by data processing, given all combinations of the assumed prevalence rates and between-variable correlations of the input symptoms.[6] There is only one exception: dysthymic disorder with the input symptoms that are randomly and 

independently present in 70% of the population. This is because the diagnosis of dysthymic disorder is a multiplicative product of the major and minor criteria. Without correlations, everyone in the population is certain to qualify for the minor criteria (probability of 100% because having at least two out of the six items in the minor criteria: mathematically [C(2,6) + C(3,6) + C(4,6) + C(5,6) + C(6,6)] X (0.7)<sup>6</sup> = 37 X 0.117 = 4.35 > 100%). If 70% of the population were also randomly assigned with the major criteria and 100% were assigned with the minor criteria, 70% would be diagnosed with dysthymic disorder, and the diagnosis of dysthymic disorder can be fully explained by the major criteria. In fact, without correlations between input symptoms, it only requires each of the six items in the minor criteria to be randomly assigned to 54.8%  $[(1/37)^{(1/6)}]$  of the population for everyone to qualify for the minor criteria, and the diagnosis can be fully explained by the minor and major criteria. 

# 17396Distortion of the input symptoms

The importance of the input symptoms has been distorted due to the diagnostic criteria for the three mental illnesses. The same phenomenon has been proven in the diagnosis of frailty based on three of the most commonly used scoring methods.[6] In other words, based on the functions to generate the diagnoses, the input symptoms are differentially weighted, and weights are not explicitly acknowledged. The most prominent is the diagnosis of dysthymic disorder; more than 90% of the variance can be explained by its major criteria assuming 0.7 or 0.9 between-variable correlations for the input symptoms in Table 6. Another example is that the third item of the major criteria for the diagnosis of manic episodes, "irritable mood," individually predicts the diagnosis better than any other input symptoms or intermediate variables. The input symptom has been given more weight than others and can explain more than 91.8% of the diagnosis variance, assuming 0.9 correlations between input symptoms. Based on the texts in the DSM-IV-TR, we do not think this symptom should be emphasized to this degree. However, the diagnostic criteria impose implicit and unequal weights to the input symptoms, and introduce biases into the diagnoses. 

### 38 412 Future directions

We think it important to rethink the role and importance of the diagnostic system. Current approaches are embedded with implicit assumptions of the prevalence rates of the diagnoses (no higher than input symptoms if similar symptom prevalence), unacknowledged weights to input symptoms (certain input symptoms explaining the diagnoses much better), and biases that were induced by data processing and could not be explained by the input symptoms. It is unclear whether the diagnosis of dysthymic disorder was intentionally designed to be more prevalent than those of major depressive episodes or manic episodes assuming input symptoms with the same prevalence rates. 

In the real world, there are other important issues related to the diagnostic criteria. For example, diagnoses are not closely linked to treatment, [19, 29] diagnoses are not well made particularly by non-psychiatrists,[30] and there are two diagnostic systems (the DSM and the International Classification of Disease) that require efforts to harmonize.[31] Amid these issues, we think the diagnostic criteria for mental illnesses should be reviewed and improved to be easier to understand and use without introducing biases, and closely linked to clinical decisions. Certain measures and biomarkers have been proven useful to identify mental illnesses.[32, 33] We are developing methods to detect symptom-based conditions better and propose methods to search for neglected mental symptoms. 

### 430 Limitations

The strength of this study is the use of simple assumptions in simulated populations that enables the comparison of the diagnostic criteria of three mental illnesses. However, the assumptions in the prevalence rates and between-variable correlations for the input symptoms might not be realistic. Some of the assumptions are unlikely to hold in the real world. However, simulations are the only option for us due to the lack of real-world data on the prevalence of the input symptoms. In addition, the translation from symptoms to diagnoses was assumed to be perfect based on the diagnostic criteria. The simulations in this study only reflect the problems in the design of the diagnostic criteria and are not designed to review the impact of how they are used in the real world. 

### **Conclusion**

To the best of our knowledge, there is no study on the relationships between the input symptoms and diagnoses. The input symptoms were extracted from the diagnostic criteria and the diagnostic criteria were transformed into mathematical functions. Without mental illness data available to the public, 100,000 subjects were simulated with different assumptions on the prevalence rates (0.05, 0.1, 0.3, 0.5, and 0.7) and correlations (0, 0.1, 0.4, 0.7, and 0.9) of the input symptoms. We found that biases were introduced into the diagnoses of three mental illnesses: major depressive episodes, dysthymic disorder, and manic episodes. The prevalence rates of the diagnoses were proportional to the assumed prevalence rates and between-variable correlations of the input symptoms. Certain input symptoms were more important than the others in explaining the diagnoses. However, the input symptoms could not fully explain the diagnoses, except when the input symptoms independent of each other with 0.7 symptom prevalence rates were used for the diagnosis of dysthymic disorder. In conclusion, the criteria used to diagnose these three mental illnesses may fail to represent the concepts they are based on, in a similar manner to three of the most commonly used scoring methods to diagnose frailty. 

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- 54 464 Not applicable

### 56 465 **Consent for publication**

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### **Data Availability**

No real-world data used - all analysis are based on simulations reproducible with the files in the supplemental materials. 

#### **Competing Interests**

YSC is currently employed by the Canadian Agency for Drugs and Technologies in Health.

The other authors have declared that no competing interests exist. 

#### **Authors' Contributions**

YSC conceptualized and designed this study, managed and analyzed data and ze KFL a. Jernent ano ( Jign of this study... drafted the manuscript. KFL assisted in the interpretation of the diagnostic criteria. CJW assisted in data management and computation. HCW, HTH, LCT, YPC, YCL, and WCC participated in the design of this study. All authors reviewed and approved the manuscript. 

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4 5			Assumptions		
6 7 8		1	Equal prevalence rates for the input symptoms of the same diagnosis; presence of input symptoms assigned randomly		
9 10 11		2	Same correlations between the input symptoms of the diagnoses of major depressive episodes and dysthymic disorder; same correlations between the input symptoms of manic episodes		
12 13		3	The input symptoms of manic episodes created independent of those of major depressive episodes and dysthymic disorder		
14 15 16		4	Diagnoses made accurately based on the diagnostic criteria and symptoms reported accurately by patients		
17 18			Parameters of input symptoms of the same diagnosis for each simulation		
19 20		1	Population sizes	10,000	
20 21 22		2	Prevalence rates (uniform for all input symptoms in a simulation)	0.05, 0.1, 0.3, 0.5, and 0.7	
23 24 25		3	Correlations (uniform between all input symptoms of the same diagnosis in a simulation)	0, 0.1, 0.4, 0.7, and 0.9	
25 26 27		4	Number of simulations for each combination of the assumed prevalence rates and between-variable correlations of the input symptoms	100	
28	570				
29 30	571				
31 32 33	572 573				
34 35 26	574 575				
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### 576 Table 2. The input symptoms, intermediate variables, and bias variables for the diagnosis of major depressive episodes.

Classification of symptoms	Criterion variable	Domains in the major or minor criteria	Domain variables	Symptoms	Symptom variables	Equations to derive diagnosis or domain variables	Approximation by linear regression	Mechanisms related to introducing biases
Major depressive episode (variable = mde)						mde = mde_ma1 x mde_ma2 x (mde_mi3 + mde_mi4 + mde_mi5 + mde_mi6 + mde_mi7 + mde_mi8 + mde_mi9 + mde_bias1) + (1- mde_ma1 x mde_ma2) x (me_ma1 x mde_ma2) x (mde_mi3 + mde_mi4 + mde_mi6 + mde_mi6 + mde_mi7 + mde_mi8 + mde_mi9 + mde_bias2)	mde = intercept + coef1 x mde_ma1 + coef2 x mde_ma2 + coef3 x mde_mi3 + coef4 x mde_mi4 + coef5 x mde_mi5 + coef6 x mde_mi6 + coef7 x mde_mi7 + coef8 x mde_mi8 + coef9 x mde_mi9 + coef10 x mde_bias	<ol> <li>Multiplication to create the situat when one or two symptoms in th major criteria confirmed and the (mde_bias) calculated by extract the information of the diagnosis explained by the input symptoms two bias variables generated by censoring (mde_bias1 and mde_bias2)</li> <li>Categorizing of the sum of the in symptoms in the minor criteria at threshold of three or four (mde_t and mde bias2)</li> </ol>
Major criteria, essential for diagnosis								_ /
		Depressed mood or a loss of interest or pleasure in daily activities for more than two weeks.						
		Depressed mood for more than two weeks	mde_ma1					
		Loss of interest or pleasure in daily activities for more than two weeks	mde_ma2					
Minor criteria (at least 5 of the symptoms including the two in maior criteria)	mde_mi							
		Significant unintentional weight loss or gain	mde_mi3			mde_mi3 = mde_mi3_1 + mde_mi3_2 + mde_mi3_bias		Censoring of the sum of multiple input variable
				Significant unintentional weight gain	mde_mi3_1			
				Significant unintentional weight loss	mde_mi3_2			
				Information of the domain not explained by the input variables	mde_mi3_bias			
		Insomnia or sleeping too much	mde_mi4			mde_mi4 = mde_mi4_1 + mde_mi4_2 + mde_mi4_bias		Censoring of the sum of multiple input variable
				Insomnia Sleeping too much	mde_mi4_1			
				Information of the domain not explained by the input variables	mde_mi4_bias			
		Agitation or psychomotor retardation noticed by others	mde_mi5			mde_mi5 = mde_mi5_1 + mde_mi5_2 + mde_mi5_bias		Censoring of the sum of multiple input variable
				Agitation	mde mi5 1			

					Psychomotor retardation noticed	mde_mi5_2		
					by others Information of the domain not	mde_mi5_bias		
					explained by the input variables			
			Fatigue or loss of energy	mde_mi6	Fatique	mde mi6 1	mde_mi6 = mde_mi6_1 + mde_mi6_2 + mde_mi6_bias	Censoring of the sum of multiple input var
					Loss of energy Information of the	mde_mi6_2 mde_mi6_bias		
					domain not explained by the			
			Feelings of worthlessness or	mde_mi7	input variables		mde_mi7 = mde_mi7_1 + mde_mi7_2 + mde_mi7_bias	Censoring of the sum of multiple input var
			CACCESSIVE guilt		Feelings of worthlessness	mde_mi7_1		
					Feelings of	mde_mi7_2		
					Information of the domain not explained by the	mde_mi7_bias		
			Diminished ability to	mde mi8	input variables		mde mi8 = mde mi8 1 + mde mi8 2	Censoring of the sum of multiple input var
			think or concentrate, or indecisiveness+	-			+ mde_mi8_bias	
					Diminished ability to think or	mde_mi8_1		
					Indecisiveness	mde_mi8_2		
					Information of the domain not explained by the	mde_mi8_bias		
			Recurrent thoughts of	mde_mi9	Input variables			
	Information due to categorization (choosing three domains in minor	mde_bias1	death					Bias introduced to categorize the sum of t number of confirmed symptoms in the min
	criteria) Information due to categorization (choosing four	mde_bias2						Bias introduced to categorize the sum of t number of confirmed symptoms in the min
	criteria) Information of diagnosis not explained by the	mde_bias						Information of the diagnosis not explained input variables and two bias variables gen due to data categorization
77	UIIIdillə							
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				F				
				For pe	er review only -	- http://bmjo	pen.bmj.com/site/about/guidelines.xhtml	

580 Table 3. The input symptoms, intermediate variables, and bias variables for the diagnosis of dysthymic disorder.

Classification of symptoms	Criterion variable	Major or minor criteria (domains)	Intermediate variables	Symptoms	Symptom variables	Equations to generate diagnosis or domain variables	Approximation	Mechanisms related to introducing biases
Dysthymia (variable = dys)						dys = dys_ma x dys_mi	dys = intercept + coef1 x dys_ma + coef2 x dys_mi + coef3 x dys_bias	Multiplication to create the situations where both the major and minor criteria met (union of two binomial variables, mde_ma x mde_mi) and the bias variable (dys_bias) equivalent to the residual of the diagnosis not explained by the input symptoms and the bias variables due to censoring and categorization
Major criteria, essential for diagnosis								
		Depressed mood most of the day for more days than not, for at least 2 years	dys_ma					
Minor criteria (at least 2 items)			dys_mi			dys_mi = dys_mi1 + dys_mi2 + dys_mi3 + dys_mi4 + dys_mi5 + dys_mi6 + dys_mi_bias		Categorizing of the sum of multiple input variables
		Poor appetite or overeating	dys_mi1			dys_mi1 = dys_mi1_1 + dys_mi1_2 + dys_mi1_bias		Censoring of the sum of multiple input variables
				Poor appetite	dys_mi1_1			
				Overeating	dys_mi1_2			
				Information of the domain not explained by the input variables	dys_mi1_bias			
		Insomnia or sleeping too much*	dys_mi2/mde_mi4			dys_mi2 = mde_mi4 = mde_mi4_1 + mde_mi4_2 + mde_mi4_bias		Censoring of the sum of multiple input variables
				Insomnia	mde_mi4_1			
				Sleeping too much	mde_mi4_2			
				domain not explained by the input variables	mde_mi4_bias			
		Low energy or fatigue*	dys_mi3/mde_mi6			dys_mi3 = mde_mi6 = mde_mi6_1 + mde_mi6_2 + mde_mi6_bias		Censoring of the sum of multiple input variables
				Fatigue	mde_mi6_1			
				Loss of energy (low energy)	mde_mi6_2			
				domain not explained by the input variables	mde_mio_blas			
		Low self-esteem Poor concentration or difficulty making decisions*	dys_mi4 dys_mi5/mde_mi8			dys_mi5 = mde_mi8 = mde_mi8_1 + mde_mi8_2 + mde_mi8_bias		Censoring of the sum of multiple input variables
				Diminished ability to think or concentrate (Poor concentration)	mde_mi8_1			
				difficulty making decisions (indecisiveness)	mde_mi8_2			
				Information of the domain not explained by the input variables	mde_mi8_bias			
		Feelings of hopelessness	dys_mi6					

			Information of minor criteria not explained	dys_mi_bias	Bias introduced by categorizing the number of input symptoms confirmed in the minor criteria
	Information of diagnosis not explained by major or minor criteria	dys_bias	by input variables		Information of the diagnosis not explained by the inpusition of the bias variables generated due to date to date the bias variables generated due to date the bias of the bias
581	*The same in	put symp	toms used for t	ne diagnosis of major depressive episode	es.
582					
				For poor rovious only http://hmionon.husi	m/site/about/quidalings/html
				For peer review only - http://bmjopen.bmj.com	m/site/about/guidelines.xntmi
584 Table 4. The input symptoms, intermediate variables, and bias variables for the diagnosis of manic episodes

symptoms	variable	(domains)	variables	Symptoms	variables		Approximation	biases	
Manic episode (variable = manic)						<pre>manic = (1- man_ma1 x man_ma2) x (man_ma1 + man_ma2) x man_ma3 x (man_mi1 + man_mi2 + man_mi3 + man_mi4 + man_mi5 + man_mi6 + man_mi7 + man_mi3s1) + [1 - (1 - man_ma1 x man_ma2)(man_ma1 + man_ma2)] x man_ma3 x (man_mi1 + man_mi2 + man_mi3 + man_mi4 + man_mi5 + man_mi6 + man_mi7 + man_bias2)</pre>	manic = intercept + coef1 x man_ma1 + coef2 x man_ma2 + coef3 x man_ma3 + coef4 x man_mi1 + coef5 x man_mi2 + coef6 x man_mi3 + coef7 x man_mi4 + coef8 x man_mi5 + coef9 x man_mi6 + coef10 x man_mi7 + coef11 x man_bias	1) 2) 3) 4)	Multiplication to creat the situations where of of the symptom in the major criteria met (un of three binomial variables, such as man_ma1 + man_ma and man_ma1 x man_ma2), In multiplication for the condition of presentir irritable mood ( x man_ma3), and the bias variable (man_bias) equivaler the residual of the diagnosis not explain by the input symptom and the bias variables introduced by categorizing the num of input symptoms confirmed in the minue confirmed in the minue confirmed in the minue
Major criteria, essential for the diagnosis of a manic episode (more than one bipolar episode required to diagnose bipolar disorder)									inen_biasz)
,		A distinct period of abnormally and persistently elevated, expansive, or irritable mood, lasting at least 1 week (or any duration if hospitalization is necessary)							
				Elevated mood, lasting at least 1 week	man_ma1				
				Expansive mood, lasting at least 1 week	man_ma2				
				Irritable mood, lasting at least 1 week	man_ma3				
Minor criteria (3 or more of the following symptoms have persisted; 4 if the mood is only irritable)									
		Increased self-esteem or grandiosity	man_mi1	Increase - I If	mon mid d	man_mi1 = man_mi1_1 + man_mi1_2 + man_mi1_bias		Censoring variables	of the sum of multiple in
				Increased self-	man_mi1_1				
				Catecini					

				Information of the domain not explained by the input variables	man_mi1_bias		
		Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)	man_mi2				
		More talkative than usual or pressure to keep talking	man_mi3			man_mi3 = man_mi3_1 + man_mi3_2 + man_mi3_bias	Censoring of the sum of m variables
				More talkative than usual	man_mi3_1		
				Pressure to keep talking Information of the domain not explained by the input variables	man_mi3_2 man_mi3_bias		
		Flight of ideas or subjective experience that thoughts are racing	man_mi4			man_mi4 = man_mi4_1 + man_mi4_2 + man_mi4_bias	Censoring of the sum of m variables
		-		Flight of ideas	man_mi4_1		
				Subjective experience that thoughts are racing	man_mi4_2		
				Information of the domain not explained by the input variables	man_mi4_bias		
		Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)	man_mi5				
		Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation	man_mi6			man_mi6 = man_mi6_1 + man_mi6_2 + man_mi6_bias	Censoring of the sum of n variables
				Increase in goal- directed activity	man_mi6_1		
				Psychomotor agitation	man_mi6_2		
				Information of the domain not explained by the input variables	man_mi6_bias		
		Excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)	man_mi7				
Information of diagnosis due to categorization (choosing at least three symptoms)	man_bias1						Bias introduced by catego number of input symptoms the minor criteria
Information of diagnosis due to categorization (choosing at least four symptoms)	man_bias2						Bias introduced by catego number of input symptoms the minor criteria
Information of diagnosis not	man_bias						Information of the diagnos explained by the input syn

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explained by symptoms		the bias variables generated due to data categorization, man_bias1 and man_bias2
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586 Table 5. The derived prevalence rates of the diagnoses of major depressive episodes, dysthymic

587 disorder, and manic episodes based on the assumed prevalence rates and between-variable correlations 588 of the input symptoms

6						
7		Assumed correlations	Assumed prevalence of	Major depressive episodes	Dysthymic disorder	Manic episodes
8		between input	input			
9		0	0.05	0 (95% CI = 0 to 0)	0.004 (95% CI = 0.004 to	0 (95% CI = 0 to 0)
10		•			0.004)	
11		0	0.1	0.001 (95%  CI = 0.001  to  0.001)	0.025 (95% CI = 0.025 to 0.025)	0.002 (95%  CI = 0.002  to  0.002)
12 12		0	0.3	0.067 (95% CI = 0.067 to 0.067)	0.249 (95% CI = 0.249 to 0.249)	0.136 (95% CI = 0.135 to 0.136)
13 14		0	0.5	0.245 (95% CI = 0.244 to 0.245)	0.493 (95% CI = 0.493 to 0.493)	0.436 (95% CI = 0.436 to 0.436)
15		0	0.7	0.49 (95% CI = 0.49 to 0.49)	0.7 (95% CI = 0.7 to 0.7)	0.692 (95% CI = 0.692 to 0.693)
16		0.1	0.05	0.004 (95% CI = 0.004 to 0.004)	0.018 (95% CI = 0.018 to	0.007 (95% CI = 0.007 to 0.007)
17		0.1	0.1	0.011 (95% CI = 0.011 to 0.011)	0.049 (95% CI = 0.049 to 0.049)	0.022 (95% CI = 0.021 to 0.022)
18		0.1	0.3	0.094 (95% CI = 0.094 to 0.094)	0.25 (95% CI = 0.25 to 0.25)	0.172 (95% CI = 0.171 to 0.172)
19		0.1	0.5	0.267 (95% CI = 0.267 to 0.268)	0.482 (95% CI = 0.482 to 0.482)	0.425 (95% CI = 0.425 to 0.425)
20		0.1	0.7	0.51 (95% CI = 0.509 to 0.51)	0.697 (95% CI = 0.697 to 0.697)	0.679 (95% CI = 0.679 to 0.679)
21 22		0.4	0.05	0.019 (95% CI = 0.019 to 0.019)	0.037 (95% CI = 0.037 to 0.037)	0.029 (95% CI = 0.029 to 0.029)
23		0.4	0.1	0.042 (95% CI = 0.042 to 0.042)	0.078 (95% CI = 0.078 to 0.078)	0.062 (95% CI = 0.062 to 0.062)
24 25		0.4	0.3	0.166 (95% CI = 0.166 to 0.167)	0.267 (95% CI = 0.267 to 0.267)	0.231 (95% CI = 0.231 to 0.231)
26		0.4	0.5	0.344 (95% CI = 0.344 to 0.344)	0.476 (95% CI = 0.476 to 0.476)	0.44 (95% CI = 0.44 to 0.441)
27		0.4	0.7	0.57 (95% CI = 0.57 to 0.57)	0.689 (95% CI = 0.688 to 0.689)	0.666 (95% CI = 0.666 to 0.666)
28 29		0.7	0.05	0.035 (95% CI = 0.035 to 0.035)	0.046 (95% CI = 0.046 to 0.046)	0.042 (95% CI = 0.042 to 0.042)
30		0.7	0.1	0.071 (95% CI = 0.071 to 0.071)	0.092 (95% CI = 0.092 to 0.092)	0.085 (95% CI = 0.085 to 0.085)
31		0.7	0.3	0.233 (95% CI = 0.233 to 0.234)	0.285 (95% CI = 0.285 to 0.285)	0.27 (95% CI = 0.27 to 0.27)
32 33		0.7	0.5	0.422 (95% CI = 0.421 to 0.422)	0.486 (95% CI = 0.485 to 0.486)	0.469 (95% CI = 0.468 to 0.469)
24		0.7	0.7	0.635 (95% CI = 0.635 to 0.635)	0.69 (95% CI = 0.69 to 0.691)	0.678 (95% CI = 0.677 to 0.678)
34 35		0.9	0.05	0.042 (95% CI = 0.042 to 0.042)	0.048 (95% CI = 0.048 to 0.048)	0.046 (95% CI = 0.046 to 0.046)
36		0.9	0.1	0.085 (95% CI = 0.085 to 0.085)	0.096 (95% CI = 0.096 to 0.097)	0.093 (95% CI = 0.093 to 0.093)
37		0.9	0.3	0.268 (95% CI = 0.268 to 0.268)	0.293 (95% CI = 0.293 to 0.293)	0.286 (95% CI = 0.286 to 0.287)
38 39		0.9	0.5	0.463 (95% CI = 0.463 to 0.463)	0.493 (95% CI = 0.492 to 0.493)	0.485 (95% CI = 0.485 to 0.486)
40		0.9	0.7	0.669 (95% CI = 0.669 to 0.669)	0.695 (95% CI = 0.694 to 0.695)	0.688 (95% CI = 0.688 to 0.688)
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## Table 6. The individual input symptoms that best explained the diagnoses: major depressive episodes, dysthymic disorder, and manic episodes

correlations between input symptoms	Assumed prevalence of input symptoms	Major depressive episodes	Dystnymic alsoraer	Manic episodes
0	0.05	mde ma1	dys ma	man ma3
0	0.05	0.001 (95% CI = 0.001 to 0.001)	0.076 (95% CI = 0.075 to 0.077)	0.002 (95% CI = 0.002 to 0
0	0.1	mde_ma1	dys_ma	man_ma3
0	0.1	0.01 (95% CI = 0.01 to 0.01)	0.228 (95% CI = 0.227 to 0.229)	0.021 (95% CI = 0.02 to 0.0
0	0.3	mde_ma1	dys_ma	man_ma3
0	0.3	0.167 (95% CI = 0.167 to 0.167)	0.774 (95% CI = 0.773 to 0.774)	0.366 (95% CI = 0.366 to 0
0	0.5	mde_ma2	dys_ma	man_ma3
0	0.5	0.324 (95% CI = 0.324 to 0.325)	0.971 (95% CI = 0.971 to 0.971)	0.773 (95% CI = 0.772 to 0
0	0.7	mde_ma2	dys_ma	man_ma3
0	0.7	0.412 (95% CI = 0.412 to 0.412)	0.999 (95% CI = 0.999 to 0.999)	0.964 (95% CI = 0.964 to 0
0.1	0.05	mde_ma2	dys_ma	man_ma3
0.1	0.05	0.07 (95% CI = 0.07 to 0.071)	0.353 (95% CI = 0.352 to 0.355)	0.136 (95% CI = 0.135 to 0
0.1	0.1	mde_ma1	dys_ma	man_ma3
0.1	0.1	0.101 (95%  CI = 0.1  to  0.101)	0.462 (95% CI = 0.461 to 0.463)	0.199 (95%  CI = 0.198  to  0
0.1	0.3	mde_ma2	dys_ma	man_ma3
0.1	0.3	0.242 (95%  CI = 0.242  to  0.243)	0.777 (95%  CI = 0.777  to  0.778)	0.483 (95% CI = 0.483 to 0
0.1	0.5	mde_ma2	dys_ma	man_ma3
0.1	0.5	0.365 (95%  CI = 0.365  to  0.366)	0.932 (95% CI = 0.931 to 0.932)	0.74 (95%  CI = 0.74  to  0.72
0.1	0.7	mde_ma2	dys_ma	man_ma3
0.1	0.7	0.445 (95%  CI = 0.445  to  0.446)	0.986 (95% CI = 0.986 to 0.986)	0.906 (95% CI = 0.906 to 0
0.4	0.05	mde_ma1	dys_ma	$man_ma3$
0.4	0.05	0.375(95%  CI = 0.373(0.0.376))	0.731(95%  CI = 0.729(0.0.732)	0.561(95%  CI = 0.559100)
0.4	0.1	0.205 (05% C) = 0.204 to 0.206)	0.762 (0.69) (0.1 - 0.762 to 0.764)	0.505 (0.5%) Cl = 0.504 to 0
0.4	0.1	0.395 (95% CI = 0.394 (0 0.396)	0.703 (95% CI = 0.702 to 0.704)	0.595 (95% CI = 0.594 10 0
0.4	0.3	0.465(05%) CI = 0.465 to 0.466)	0.851 (05% C) = 0.85 to 0.851)	0.701 (05% C) = 0.701 to 0
0.4	0.5	0.403 (93 % CI = 0.403 to 0.400)	due ma	0.701 (95% CI = 0.701 to 0
0.4	0.5	0.525(95%  Cl = 0.524  to  0.525)	0.908 (95% C) = 0.908 to 0.908)	0.787 (95%  Cl = 0.786  to  0
0.4	0.5	mde ma2	dvs ma	man ma3
0.4	0.7	0.568(95%  Cl = 0.568  to  0.569)	0.946(95%  Cl = 0.946  to  0.947)	0.855 (95%  Cl = 0.854  to  0.000  cl
0.4	0.05	mde ma2	dvs ma	man ma3
0.7	0.05	0.688(95%  CL = 0.687  to  0.69)	0.909(95%  Cl = 0.908  to  0.909)	0.831 (95%  Cl = 0.83  to  0.83  t
0.7	0.00	mde ma1	dvs ma	man ma3
0.7	01	0.688(95%  Cl = 0.687  to  0.689)	0.912 (95%  CI = 0.911  to  0.913)	0.836 (95%  Cl = 0.835  to  0
0.7	0.3	mde ma2	dys ma	man ma3
0.7	0.3	0.71(95%  Cl = 0.709  to  0.711)	0.93(95%  Cl = 0.93  to  0.93)	0.862(95%  Cl = 0.861  to  0.862(95%  Cl = 0.861)
0.7	0.5	mde ma2	dvs ma	man ma3
0.7	0.5	0.729 (95% CI = 0.728 to 0.729)	0.944 (95% CI = 0.943 to 0.944)	0.882 (95% CI = 0.882 to 0
0.7	0.7	mde ma1	dys ma	man ma3
0.7	0.7	0.745 (95% CI = 0.744 to 0.745)	0.954 (95% CI = 0.954 to 0.955)	0.9 (95% CI = 0.9 to 0.9)
0.9	0.05	mde_ma1	dys_ma	man_ma3
0.9	0.05	0.828 (95% CI = 0.827 to 0.829)	0.958 (95% CI = 0.957 to 0.958)	0.918 (95% CI = 0.917 to 0
0.9	0.1	mde_ma2	dys_ma	man_ma3
0.9	0.1	0.838 (95% CI = 0.838 to 0.839)	0.961 (95% CI = 0.961 to 0.961)	0.925 (95% CI = 0.924 to 0
0.9	0.3	mde_ma2	dys_ma	man_ma3
0.9	0.3	0.856 (95% CI = 0.856 to 0.857)	0.969 (95% CI = 0.968 to 0.969)	0.937 (95% CI = 0.936 to 0
0.9	0.5	mde_ma2	dys_ma	man_ma3
0.9	0.5	0.862 (95% CI = 0.862 to 0.863)	0.972 (95% CI = 0.972 to 0.972)	0.942 (95% CI = 0.942 to 0
0.9	0.7	mde_ma2	dys_ma	man_ma3
0.9	0.7	0.865 (95% CI = 0.865 to 0.866)	0.974 (95% CI = 0.974 to 0.974)	0.946 (95% CI = 0.946 to 0

Assumed correlations between input _symptoms	Assumed prevalence of input symptoms	Major depressive episodes	Dysthymic disorder	Manic episodes
0	0.05	mde_bias2	dys_bias	man_bias2
0	0.05	0 (95% CI = 0 to 0)	0.028 (95% CI = 0.028 to 0.028)	0.001 (95% CI = 0.001
0	0.1	mde_bias2	dys_bias	man_bias2
0	0.1	0.004 (95% CI = 0.004 to 0.004)	0.053 (95% CI = 0.053 to 0.054)	0.011 (95% CI = 0.011
0	0.3	mde_bias2	dys_bias	man_bias1
0	0.3	0.015 (95% CI = 0.015 to 0.015)	0.045 (95% CI = 0.045 to 0.045)	0.089 (95% CI = 0.089
0	0.5	$nde_{Dias}$	0.007 (0.5%) = 0.007 to 0.007)	$man_{Dlas1}$
0	0.5	0.013 (95% CI = 0.013 (0 0.014)	0.007 (95% CI = 0.007 (0 0.007)	0.035 (95% CI = 0.034
0	0.7	0.01(95%  Cl = 0.01  to  0.01)	0.(95%  Cl = 0  to  0)	0.002(95%  Cl = 0.002)
0 1	0.05	mde bias2	dvs bias	man_bias1
0.1	0.05	0.037 (95%  Cl = 0.037  to  0.037)	0.113 (95%  Cl = 0.113  to  0.114)	0.083 (95%  Cl = 0.083)
0.1	0.1	mde bias2	dvs bias	man bias1
0.1	0.1	0.047 (95% CI = 0.047 to 0.048)	0.122 (95% CI = 0.121 to 0.122)	0.116 (95% CI = 0.115
0.1	0.3	mde_bias2	dys_mi_bias	man_bias1
0.1	0.3	0.077 (95% CI = 0.077 to 0.077)	0.105 (95% CI = 0.105 to 0.106)	0.198 (95% CI = 0.197
0.1	0.5	mde_bias2	dys_mi_bias	man_bias1
0.1	0.5	0.079 (95% CI = 0.079 to 0.08)	0.073 (95% CI = 0.073 to 0.073)	0.166 (95% CI = 0.166
0.1	0.7	mde_bias2	dys_mi_bias	man_bias1
0.1	0.7	0.065 (95% CI = 0.065 to 0.065)	0.047 (95% CI = 0.046 to 0.047)	0.094 (95% CI = 0.093
0.4	0.05	mde_bias1	dys_mi_bias	man_bias1
0.4	0.05	0.294 (95% CI = 0.293 to 0.295)	0.415 (95% CI = 0.413 to 0.416)	0.432 (95% CI = 0.43
0.4	0.1	$nde_blas_1$ 0.204 (05% Cl = 0.202 to 0.204)	$dys_m_blas$	$man_{Dias1}$
0.4	0.1	mde bias1	dvs mi bias	man_bias1
0.4	0.3	0.335 (95%  Cl = 0.334  to  0.335)	0.411 (95%  Cl = 0.411  to  0.412)	0.473(95%  Cl = 0.473)
0.4	0.5	mde bias1	dvs mi bias	man bias1
0.4	0.5	0.354 (95%  Cl = 0.354  to  0.355)	0.395 (95%  Cl = 0.395  to  0.396)	0.475 (95% CI = 0.474
0.4	0.7	mde bias1	dys mi bias	man bias1
0.4	0.7	0.356 (95% CI = 0.355 to 0.356)	0.367 (95% CI = 0.366 to 0.367)	0.451 (95% CI = 0.45
0.7	0.05	mde_bias1	dys_mi_bias	man_bias1
0.7	0.05	0.616 (95% CI = 0.615 to 0.617)	0.705 (95% CI = 0.704 to 0.706)	0.723 (95% CI = 0.722
0.7	0.1	mde_bias1	dys_mi_bias	man_bias1
0.7	0.1	0.611 (95% CI = 0.611 to 0.612)	0.699 (95% CI = 0.698 to 0.699)	0.72 (95% CI = 0.72 to
0.7	0.3	mde_blas1	dys_mi_bias	man_bias1
0.7	0.3	0.023 (95% CI = 0.623 to 0.624)	0.099 (95% CI = 0.699 to 0.7)	0.728 (95% CI = 0.728
0.7	0.5	0.632 (95%  CI = 0.632  to  0.633)	-0.696(95%  Cl = 0.696  to  0.697)	0.731 (95%  Cl = 0.73)
0.7	0.5	mde bias1	dvs mi bias	man bias1
0.7	0.7	0.639 (95%  CI = 0.638  to  0.639)	0.693 (95%  Cl = 0.692  to  0.693)	0.732 (95%  Cl = 0.73)
0.9	0.05	mde bias1	dys mi bias	man bias1
0.9	0.05	0.777 (95% CI = 0.776 to 0.778)	0.835 (95% CI = 0.834 to 0.835)	0.847 (95% CI = 0.847
0.9	0.1	mde_bias1	dys_mi_bias	man_bias1
0.9	0.1	0.788 (95% CI = 0.788 to 0.789)	0.842 (95% CI = 0.841 to 0.843)	0.855 (95% CI = 0.854
0.9	0.3	mde_bias1	dys_mi_bias	man_bias1
0.9	0.3	0.807 (95% CI = 0.806 to 0.807)	0.854 (95% CI = 0.853 to 0.854)	0.867 (95% CI = 0.867
0.9	0.5	mde_bias1	dys_mi_bias	man_bias1
0.9	0.5	0.811 (95% CI = 0.811 to 0.811)	0.855 (95%  CI = 0.855  to  0.856)	0.87 (95% CI = 0.87 to
0.9	0.7	mae_blas1	0.852 (05% CL = 0.952 to 0.952)	
0.9	U.7	0.012 (95%  CI = 0.811  to  0.812)	0.653 (95% CI = 0.853 to 0.853)	0.009 (95% CI = 0.869

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612	Table 8. Approximating	the diagnoses	using input symptoms	and derived adjusted R-
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	Assumed correlations between input symptoms	Assumed prevalence of input symptoms	Major depressive episodes	Dysthymic disorder	Manic episodes
	0	0.05	0.003 (95% CI = 0.002 to 0.003)	0.122 (95% CI = 0.121 to 0.123)	0.004 (95% CI = 0.004 to 0.0
	0	0.1	0.024 (95% CI = 0.023 to 0.024)	0.305 (95% CI = 0.304 to 0.306)	0.039 (95% CI = 0.038 to 0.0
	0	0.3	0.348 (95% CI = 0.348 to 0.349)	0.842 (95% CI = 0.841 to 0.842)	0.483 (95% CI = 0.482 to 0.4
	0	0.5	0.649 (95% CI = 0.649 to 0.649)	0.986 (95% CI = 0.986 to 0.986)	0.817 (95% CI = 0.817 to 0.8
	0	0.7	0.823 (95% CI = 0.823 to 0.823)	1 (95% CI = 1 to 1)	0.967 (95% CI = 0.967 to 0.9
	0.1	0.05	0.143 (95% CI = 0.141 to 0.144)	0.435 (95% CI = 0.433 to 0.436)	0.212 (95% CI = 0.211 to 0.2
	0.1	0.1	0.198 (95% CI = 0.197 to 0.199)	0.539 (95% CI = 0.538 to 0.54)	0.29 (95% CI = 0.289 to 0.29
	0.1	0.3	0.45 (95% CI = 0.45 to 0.451)	0.826 (95% CI = 0.826 to 0.827)	0.588 (95% CI = 0.588 to 0.5
	0.1	0.5	0.663 (95% CI = 0.663 to 0.664)	0.952 (95% CI = 0.952 to 0.952)	0.799 (95% CI = 0.799 to 0.7
	0.1	0.7	0.809 (95% CI = 0.809 to 0.809)	0.991 (95% CI = 0.991 to 0.991)	0.922 (95% CI = 0.922 to 0.9
	0.4	0.05	0.587 (95% CI = 0.585 to 0.588)	0.782 (95% CI = 0.781 to 0.783)	0.675 (95% CI = 0.674 to 0.6
	0.4	0.1	0.607 (95% CI = 0.606 to 0.608)	0.807 (95% CI = 0.807 to 0.808)	0.698 (95% CI = 0.697 to 0.6
	0.4	0.3	0.688 (95% CI = 0.688 to 0.689)	0.878 (95% CI = 0.877 to 0.878)	0.775 (95% CI = 0.774 to 0.7
	0.4	0.5	0.761 (95% CI = 0.761 to 0.762)	0.925 (95% CI = 0.924 to 0.925)	0.838 (95% CI = 0.838 to 0.8
	0.4	0.7	0.821 (95% CI = 0.821 to 0.822)	0.956 (95% CI = 0.956 to 0.956)	0.887 (95% CI = 0.887 to 0.8
	0.7	0.05	0.813 (95% CI = 0.812 to 0.814)	0.925 (95% CI = 0.925 to 0.926)	0.877 (95% CI = 0.877 to 0.8
	0.7	0.1	0.826 (95% CI = 0.826 to 0.827)	0.928 (95% CI = 0.927 to 0.928)	0.881 (95% CI = 0.881 to 0.8
	0.7	0.3	0.86 (95% CI = 0.86 to 0.86)	0.942 (95% CI = 0.942 to 0.942)	0.9 (95% CI = 0.9 to 0.9)
	0.7	0.5	0.88 (95% CI = 0.88 to 0.88)	0.953 (95% CI = 0.953 to 0.953)	0.913 (95% CI = 0.913 to 0.9
	0.7	0.7	0.895 (95% CI = 0.895 to 0.895)	0.962 (95% CI = 0.962 to 0.962)	0.925 (95% CI = 0.925 to 0.9
	0.9	0.05	0.903 (95% CI = 0.903 to 0.904)	0.965 (95% CI = 0.965 to 0.966)	0.941 (95% CI = 0.94 to 0.94
	0.9	0.1	0.91 (95% CI = 0.91 to 0.911)	0.968 (95% CI = 0.968 to 0.968)	0.945 (95% CI = 0.945 to 0.9
	0.9	0.3	0.923 (95% CI = 0.923 to 0.923)	0.974 (95% CI = 0.974 to 0.974)	0.954 (95% CI = 0.953 to 0.9
	0.9	0.5	0.928 (95% CI = 0.928 to 0.928)	0.976 (95% CI = 0.976 to 0.977)	0.958 (95% CI = 0.957 to 0.9
	0.9	0.7	0.932 (95% CI = 0.932 to 0.932)	0.978 (95% CI = 0.978 to 0.978)	0.96 (95% CI = 0.96 to 0.96)
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3	617	Table 9. App	roximating th	ne diagnoses using bia	s variables and derived	R-squared
4		Assumed	Assumed	Major depressive episodes	Dysthymic disorder	Manic episodes
5		between input	input			
6		symptoms	symptoms			
7		0	0.05	0.003 (95% CI = 0.002 to 0.003)	0.029 (95% CI = 0.029 to 0.03)	0.004 (95% CI = 0.004 to 0.004)
8		0	0.1	0.013 (95% CI = 0.012 to 0.013)	0.056 (95% CI = 0.056 to 0.056)	0.017 (95%  CI = 0.017  to  0.017)
9		0	0.3	0.083 (95% CI = 0.083 to 0.083)	0.047 (95% CI = 0.047 to 0.047)	0.098 (95% CI = 0.098 to 0.099)
10		0	0.5	0.111 (95% CI = 0.111 to 0.112)	0.007 (95% CI = 0.007 to 0.007)	0.039 (95% CI = 0.038 to 0.039)
12		0	0.7	0.095 (95% CI = 0.095 to 0.095)	0 (95% CI = 0 to 0)	0.012 (95% CI = 0.012 to 0.013)
12		0.1	0.05	0.083 (95% CI = 0.082 to 0.084)	0.145 (95% CI = 0.144 to 0.146)	0.126 (95% CI = 0.125 to 0.127)
14		0.1	0.1	0.096 (95% CI = 0.095 to 0.097)	0.156 (95% CI = 0.155 to 0.156)	0.154 (95% CI = 0.153 to 0.154)
15		0.1	0.3	0.145 (95% CI = 0.144 to 0.145)	0.139 (95% CI = 0.138 to 0.139)	0.216 (95% CI = 0.216 to 0.216)
16 17		0.1	0.5	0.172 (95% CI = 0.172 to 0.173)	0.097 (95% CI = 0.097 to 0.097)	0.182 (95% CI = 0.181 to 0.182)
18		0.1	0.7	0.175 (95% CI = 0.175 to 0.175)	0.065 (95% CI = 0.064 to 0.065)	0.115 (95% CI = 0.115 to 0.116)
19		0.4	0.05	0.421 (95% CI = 0.419 to 0.423)	0.455 (95% CI = 0.453 to 0.456)	0.505 (95% CI = 0.504 to 0.506)
20 21		0.4	0.1	0.422 (95% CI = 0.421 to 0.423)	0.454 (95% CI = 0.453 to 0.455)	0.507 (95% CI = 0.506 to 0.508)
22		0.4	0.3	0.435 (95% CI = 0.434 to 0.435)	0.442 (95% CI = 0.442 to 0.443)	0.512 (95% CI = 0.512 to 0.513)
23		0.4	0.5	0.452 (95% CI = 0.452 to 0.453)	0.427 (95% CI = 0.427 to 0.427)	0.506 (95% CI = 0.505 to 0.506)
24 25		0.4	0.7	0.46 (95% CI = 0.459 to 0.46)	0.403 (95% CI = 0.402 to 0.403)	0.481 (95% CI = 0.481 to 0.482)
26		0.7	0.05	0.728 (95% CI = 0.727 to 0.729)	0.729 (95% CI = 0.728 to 0.731)	0.764 (95% CI = 0.763 to 0.765)
27		0.7	0.1	0.722 (95% CI = 0.721 to 0.723)	0.723 (95% CI = 0.722 to 0.724)	0.76 (95% CI = 0.759 to 0.761)
28 29		0.7	0.3	0.726 (95% CI = 0.726 to 0.727)	0.722 (95% CI = 0.722 to 0.723)	0.761 (95% CI = 0.761 to 0.762)
20		0.7	0.5	0.732 (95% CI = 0.731 to 0.732)	0.72 (95% CI = 0.719 to 0.72)	0.76 (95% CI = 0.76 to 0.761)
31		0.7	0.7	0.737 (95% CI = 0.736 to 0.737)	0.717 (95% CI = 0.716 to 0.717)	0.758 (95% CI = 0.758 to 0.759)
32		0.9	0.05	0.852 (95% CI = 0.851 to 0.853)	0.85 (95% CI = 0.849 to 0.851)	0.871 (95% CI = 0.871 to 0.872)
33		0.9	0.1	0.86 (95% CI = 0.859 to 0.861)	0.857 (95% CI = 0.856 to 0.857)	0.876 (95% CI = 0.876 to 0.877)
34		0.9	0.3	0.872 (95% CI = 0.871 to 0.872)	0.867 (95% CI = 0.867 to 0.868)	0.886 (95% CI = 0.886 to 0.886)
35		0.9	0.5	0.874 (95% CI = 0.874 to 0.875)	0.869 (95% CI = 0.868 to 0.869)	0.888 (95% CI = 0.887 to 0.888)
30 37		0.9	0.7	0.874 (95% CI = 0.874 to 0.875)	0.867 (95% CI = 0.866 to 0.867)	0.886 (95% CI = 0.886 to 0.886)

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619	Figure 1. The prevalence rates of an intermediate variable for the diagnosis of major
620	depressive episodes.

622 Note: The intermediate variable is *"significant unintentional weight loss or gain"* and the input

- 623 symptoms are "significant unintentional weight loss" and "significant unintentional weight
   624 gain." The black line represents the situation where the prevalence rates of the input
- <sup>12</sup> 625 symptoms are the same as that of the intermediate variable. Lines above the black lines
- $^{13}_{14}$  626 have prevalence rates larger than those of the input symptoms.

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3 4	629	Figure 2. The prevalence rates of dysthymic disorder.
5 6	630	
7	631	Note: Dysthymic disorder is diagnosed when both the major (depressed mood most of the
8 9	632	day for more days than not, for at least 2 years) and minor criteria (at least two of the six
10	633	items) are confirmed. The black line represents the situation where the prevalence rates of
11	634	the input symptoms are the same as those of the intermediate variable. Lines below the
12 13	635	black lines have prevalence rates lower than those of the input symptoms.
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639	Figure 3. The prevalence rates of major depressive episodes.
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641	Note: Major depressive episodes are diagnosed when both major and minor criteria are
642	confirmed. The black line represents the situation where the prevalence rates of the input
6/3	symptoms are the same as that of the intermediate variable. I ines below the black lines
644	by a providence rates lower then these of the input symptome
644	have prevalence rates lower than those of the input symptoms.
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3 ⊿	648	Figure 4. The prevalence rates of manic episodes
- 5 6	649	
7	650	Note: Manic episodes are diagnosed when the symptoms present as described in the
8	651	diagnostic manual. The black line represents the situation where the prevalence rates of the
9	652	input symptoms are the same as those of the input symptoms. Lines below the black lines
10 11	653	have prevalence rates lower than those of the input symptoms.
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Figure 5. The approximation of the diagnosis of dysthymic disorder by the input symptoms, the bias 657 658 variables, and both, measured by R-squared

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> Note: the diagnosis of dysthymic disorder is approximated by the input symptoms, the bias 660 variables, and both using forward-stepwise regression. The selection of the variables was 661 determined by adjusted R-squared. See Table 4 for the details in the input symptoms and 662 the bias variables. The assumed correlations between the input symptoms are 0.4 and the 663 assumed prevalence rates of the input symptoms are 0.7. 664

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Numbers of variables

## A simulation study to demonstrate the biases in the diagnoses of mental illnesses: major depressive episodes, dysthymia, and manic episodes

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Keywords: Frailty; bias; forward-stepwise regression; the Health and Retirement Study; index mining

Mental Elnes Elness variz	labClassificationCriterion variMajor or minDomain	urisSymptoms Symptom varEquations Approximation Assumed pre}	Derived prev definition variable R	firmali cole autores subscarse
Major Depresmde	Major criteria, essential for diagnosis Decressed movel or a	mde = mde_mde = intercept + coef1 x mde_ma1 + coef2 x mde_r	na2 + coef3 x Major Deprende Major criteria Depressed mood or a loss of inter	and a regular data factor and a regular data
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		Significant unmde_mi3_2 = rbinom(ref: 0.4.)	Significant ur mde_mi1_2	na ja ja vaskaja maja na ja na ja Na ja na j
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		Psychomotormde_mi5_2 = rbinom(n+: 0.4 )	Psychomotormde_mi5_2	ماریخ استان می از این از ا
	Fatigue or losmde_mi	information onde_mi5_bias mde_mi6_1 + mde_mi6_1 + mde_mi6_2 + mde_mi6_bias fatigue mde_mi6_1 = tbinom(m: 0.4 )	Information (mde_mi5_bias Fatigue or lormde_mi5 Fatigue mde_mi5_1	
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	Feelings of winde_mi	information onde_mi6_bias mde_mi7 = mde_mi7_1 + mde_mi7_2 + mde_mi7_bias Feelings of wonde_mi7_1 = tbincm(m' 0.4 )	Information (mde_mi6_bias Feelings of winde_mi7_ Feelings of winde_mi7_1	
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		indecisiveneurode_mill_2 = rbinom(ret: 0.4.)	indecisivenesmde_mill_2	In , and a description of the second se
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		Poor appetitisdyn_mil_1         = rbinom(rn: 0.4 )           Oversating dyn_mil_2         = rbinom(rn: 0.4 )	Poor appetitishys_mi1_1 Overeating dys_mi1_2	40,123 - modge.ratio 4, sec.1 -
	Insomnia or sdys_mi2	Information odys_mi2_blas dys_mi2 = mde_mi4 = mde_mi4_1 + mde_mi4_2 + mde_mi4_bla	Information (dys_mi1_bias Insomnia or (mde_mi4	
		Insomnia mde_mi4_1 = rbinom(rv: 0.4 ) Seeping too mde_mi4_2 = rbinom(rv: 0.4 )	Insomnia mde_mi4_1 Sleeping too mde_mi4_2	na magi suddar gina Andra 2 - unddar yw Wynadaw an 1 a wafana wr 27-8
	Low energy odys_mi3	information onde_mi4_bias dys_mi3 = mde_mi6 = mde_mi6_1 + mde_mi6_2 + mde_mi6_bia	Information (mde_mi4_bias Low energy cmde_mi6	nda, artikazatea araka
		Fatigue mde_mi6_1 = rbinom(m: 0.4 ) Loss of energende_mi6_2 = rbinom(m: 0.4 )	Fatigue mde_mi6_1 Loss of energmde_mi6_2	na na set i una dese dese na dese de la constance de la constance na dese de la constance de la Constance de la constance de la const
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	Poor concentidys_mi5	dys_mi5 = mde_mi8_= mde_mi8_1 = mde_mi8_2 = mde_mi8_2 = mde_mi8_2 = mde_mi8_1 = mde_mi8_2 = mde_mi8_2 = mbinom(mr: 0.4 ) dffoulty makende_mi8_2 = mbinom(mr: 0.4 )	Poor concentrade_mill Diminished a mde_mill_1 difficulty maimde_mill_2	
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	Miner criteria (2 or more of the followir	Expansive moman_ma2 = rbinom(m: 0.1) irritable moorman_ma3 = rbinom(m: 0.1) im have certified 4 if the mood is only irritable <sup>1</sup>	Espansive moman_ma2 Initable mooman_ma3 Minor criterio	na, un'a rendem, nanez
	increased selman_mi	man_mil = man_mil_1 + man_mil_2 + man_mil_bias increased selman_mil_1 = rbinom(m: 0.1)	increased selman_mi1 increased selman_mi1_1	angad Vilangadi ang ang at
		Grandiosity man_ml1_2 = rbinom(n=: 0.1 ) Information onan_ml1_bias	Grandiosity man_mi1_2 Information (man_mi1_bi==	ang hat under grinten ang all
	Decreased neman_mi More talkatieman_mi	= rbissen(m: 0.1) man_mi3=man_mi3_1+man_mi3_2+man_mi3_bias	Decreased normat_mi2 More talkathman_mi3	na je fradom jetom na
		More talkativman_mi3_1 = rbinom(m: 0.1) Pressure to kman_mi3_2 = rbinom(m: 0.1)	More talkativman_mi3_1 Pressure to k man_mi3_2	an Agi Judong Antan ang Ali Ang Judong Antan Agi Ali Ang Ali Ang Ali Ang Ali
	Right of ideaman_mi	Information oran_mi3_bias man_mi4_1 + man_mi4_2 + man_mi4_bias	Information (man_mi3_bias Flight of idea man_mi4	
		Flight of ideaman_mH_1         = rbinom(m: 0.1)           Subjective exman_mH_2         = rbinom(m: 0.1)	Flight of idea man_mi4_1 Subjective exman_mi4_2	an and index mean and at a second sec
	Distract bilityman_mi	information on an_mi4_bias = rbinom(m: 0.1 )	Information (man_mi4_bias Distractibility man_mi5	na un di haddan persona na pula
	Increase in goman_mi	man_mi5 = man_mi5_1 + man_mi5_2 + man_mi5_bias Increase in gonan_mi5_1 = + thionom(n+ 0.1) Patchanatorman_mi5_2 = + thionomian 0.1	Increase in grman_mi6 Increase in grman_mi6_1 Psychotrythorman_mi6_2	an,at'i'ilina,at,ana an,at an,at'i adamata an,at at
		Information oran_mi6_blas	Information (man_mi6_bias	nolou, jul - Yujio Kang, M. J. and Kang, M. J. 2019 manyal, kulondon gamma ma, and
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```
title: "2019_09_06 simulated mental illnesses"
author: "Yi-Sheng Chao"
date: "November 22, 2018"
output: pdf_document
editor_options:
 chunk_output_type: inline
##Adding correlations to the random variables
```{r}
library(bindata)
library(openxlsx)
resu = read.xlsx("A simulation study to demonstrate the biases in three
diagnoses of mental illnesses.xlsx", sheet = "Prob 1")
names(resu)
unique(resu$variable)
memory.limit(size = 10^13)
ssize = 10^{5}
times = 10^2
prevalence = c(0.05, 0.1, 0.3, 0.5, 0.7)
rho = c(0, 0.1, 0.4, 0.7, 0.9)#correlation coefficients of the input
symptoms
collect = c("mean", "max",
"min", "derivedprevalence", "coef", "coefse", "p", "intercept",
"interceptp", "r2", "subcoef", "subcoefse", "subp", "subintercept",
"subinterceptp","subr2", "appbyownr2", //appbybiasr2", "appbyallr2",
"appbyownvar", "appbybiasvar", "appbyallvar", "appbyownn", "appbybiasn",
"appbyalln")
set.seed(1)
##Create a simulated data set to extract variables
for(preval in 1:length(prevalence)){
  for(rh in 1:length(rho)){
  library(openxlsx)
resu = read.xlsx("A simulation study to demonstrate the biases in three
diagnoses of mental illnesses.xlsx", sheet = "Prob 1")
    # foreach(c = 1:times) %dopar% {
    for(c in 1:times){
library(bindata)
bindata = as.data.frame(rmvbin(ssize, rep(prevalence[preval], 40),
bincorr=(1 - rho[rh])*diag(40) + rho[rh]))
bindata2 = as.data.frame(rmvbin(ssize, rep(prevalence[preval], 20),
bincorr=(1 - rho[rh])*diag(20) + rho[rh]))
##demographic characteristics
```

```
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3
          sim = data.frame(1:ssize)
4
          names(sim) = "id"
5
          sim$female = rbinom(n = ssize, size = 1, prob = 0.51)
6
          sim$age = sample(30:60, ssize, replace = TRUE)
7
          sim$edu = rnorm(ssize, mean = 12, sd = 5)
8
          sim edu[which(sim edu <= 0)] = 0
9
          sim$id = NULL
10
11
12
          sim$mde_ma1 = bindata[,1]
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          sim$mde_ma2 = bindata[,2]
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          sim$mde_mi3_1 = bindata[,3]
16
          sim$mde_mi3_2 = bindata[,4]
17
          sim$mde_mi3 = 1*((sim$mde_mi3_1 + sim$mde_mi3_2) > 0)
18
          sim$mde_mi3_bias = sim$mde_mi3 - sim$mde_mi3_1 - sim$mde_mi3_2
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20
          sim$mde mi4 1 = bindata[,5]
21
          sim$mde mi4 2 = bindata[,6]
22
          sim$mde_mi4 = 1*((sim$mde_mi4_1 + sim$mde_mi4_2) > 0)
23
          sim$mde_mi4_bias = sim$mde_mi4 - sim$mde_mi4_1 - sim$mde_mi4_2
24
25
          sim$mde_mi5_1 = bindata[,7]
26
          sim$mde_mi5_2 = bindata[,8]
27
          sim$mde_mi5 = 1*((sim$mde_mi5_1 + sim$mde_mi5_2) > 0)
28
          sim$mde_mi5_bias = sim$mde_mi5 - sim$mde_mi5_1 - sim$mde_mi5_2
29
30
          sim$mde_mi6_1 = bindata[,9]
31
          sim$mde_mi6_2 = bindata[,10]
32
          sim$mde_mi6 = 1*((sim$mde_mi6_1 + sim$mde_mi6_2) > 0)
33
          sim$mde_mi6_bias = sim$mde_mi6 - sim$mde_mi6_1 - sim$mde_mi6_2
34
35
          sim$mde_mi7_1 = bindata[,11]
36
          sim mde mi7 2 = bindata[,12]
37
          sim$mde_mi7 = 1*((sim$mde_mi7_1 + sim$mde_mi7_2) > 0)
38
          sim$mde mi7 bias = sim$mde mi7 - sim$mde mi7 1 - sim$mde mi7 2
39
40
          sim$mde mi8 1 = bindata[,13]
41
          sim$mde_mi8_2 = bindata[,14]
42
          sim$mde_mi8 = 1*((sim$mde_mi8_1 + sim$mde_mi8_2) > 0)
43
          sim$mde_mi8_bias = sim$mde_mi8 - sim$mde_mi8_1 - sim$mde_mi8_2
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          sim$mde_mi9 = bindata[,15]
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          sim$mde_bias1 = 1 * ((sim$mde_mi3 + sim$mde_mi4 + sim$mde_mi5 +
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          sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9)>2) - (sim$mde_mi3
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          + sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 +
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          sim$mde mi9)
51
          sim$mde bias2 = 1 * ((sim$mde mi3 + sim$mde mi4 + sim$mde mi5 +
52
          sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9)>3) - (sim$mde_mi3
53
          + sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 +
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          sim$mde_mi9)
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56
          sim$mde = sim$mde_ma1 * sim$mde_ma2 * (sim$mde_mi3 + sim$mde_mi4 +
57
          sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9 +
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          sim$mde_bias1) + (1- sim$mde_ma1 * sim$mde_ma2) * (sim$mde_ma1 *
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          sim$mde_ma2) * (sim$mde_mi3 + sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 +
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          sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9 + sim$mde_bias2)
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sim$mde_bias = sim$mde - (sim$mde_ma1 + sim$mde_ma2) - (sim$mde_mi3 +
sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 +
sim$mde_mi9 + sim$mde_bias1) - (sim$mde_bias2)
##Definition Below: even the bias and own input variables could not fully
explain the diagnosis
# sim$mde bias = sim$mde - (sim$mde mi3 + sim$mde mi4 + sim$mde mi5 +
sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 + sim$mde_mi9 + sim$mde_bias1) -
(sim$mde_mi3 + sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 +
sim$mde_mi8 + sim$mde_mi9 + sim$mde_bias2)
# sim$mde_bias = sim$mde - (sim$mde_ma1 + sim$mde_ma2 + sim$mde_mi3 +
sim$mde_mi4 + sim$mde_mi5 + sim$mde_mi6 + sim$mde_mi7 + sim$mde_mi8 +
sim$mde_mi9)
# sim$mde_bias = resid(lm(sim$mde ~ sim$mde_ma1 + sim$mde_ma2 +
sim$mde mi3 + sim$mde mi4 + sim$mde mi5 + sim$mde mi6 + sim$mde mi7 +
sim$mde_mi8 + sim$mde_mi9, data=sim))
##DYS
sim$dys_ma = bindata[,16] `
sim$dys mi1 1 = bindata[,17]
sim$dys mi1 2 = bindata[,18]
sim$dys_mi1 = 1*((sim$dys_mi1_1 + sim$dys_mi1_2) > 0)
sim$dys_mi1_bias = sim$dys_mi1 - sim$dys_mi1_1 - sim$dys_mi1_2
sim$dys_mi4 = bindata[,19]
sim$dys_mi6 = bindata[,20]
sim$dys_mi = 1*((sim$dys_mi1 + sim$mde_mi4 + sim$mde_mi6 + sim$dys_mi4 +
sim$mde_mi8 + sim$dys_mi6)>1)
sim$dys_mi_bias = sim$dys_mi - (sim$dys_mi1 + sim$mde_mi4 + sim$mde_mi6 +
sim$dys_mi4 + sim$mde_mi8 + sim$dys_mi6)
sim$dys = sim$dys_ma * sim$dys_mi
sim$dys_bias = sim$dys - (sim$dys_ma + sim$dys_mi)
# sim$dys_bias = resid(lm(sim$dys ~ sim$dys_ma + sim$dys_mi, data=sim))
##Manic
sim$man_ma1 = bindata2[,1]
sim$man_ma2 = bindata2[,2]
sim$man_ma3 = bindata2[,3]
sim$man_mi1_1 = bindata2[,4]
sim$man_mi1_2 = bindata2[,5]
sim$man_mi1 = 1*((sim$man_mi1_1 + sim$man_mi1_2) >0)
sim$man_mi1_bias = sim$man_mi1 - (sim$man_mi1_1 + sim$man_mi1_2)
sim$man_mi2 = bindata2[,6]
```

```
2
3
          sim$man_mi3_1 = bindata2[,7]
4
          sim$man_mi3_2 = bindata2[,8]
5
          sim$man_mi3 = 1*((sim$man_mi3_1 + sim$man_mi3_2) > 0)
6
          sim$man_mi3_bias = sim$man_mi3 - (sim$man_mi3_1 + sim$man_mi3_2)
7
          sim$man_mi4_1 = bindata2[,9]
8
          sim$man mi4 2 = bindata2[,10]
9
          sim$man_mi4 = 1*((sim$man_mi4_1 + sim$man_mi4_2) > 0)
10
          sim$man_mi4_bias = sim$man_mi4 - (sim$man_mi4_1 + sim$man_mi4_2)
11
          sim$man_mi5 = bindata2[,11]
12
          sim$man_mi6_1 = bindata2[,12]
13
          sim$man_mi6_2 = bindata2[,13]
14
          sim$man_mi6 = 1*((sim$man_mi6_1 + sim$man_mi6_2) > 0)
15
          sim$man_mi6_bias = sim$man_mi6 - (sim$man_mi6_1 + sim$man_mi6_2)
16
          sim$man_mi7 = bindata2[,14]
17
          sim$man_bias1 = 1*((sim$man_mi1 + sim$man_mi2 + sim$man_mi3 + sim$man_mi4
18
          + sim$man mi5 + sim$man mi6 + sim$man mi7) > 2) - (sim$man mi1 +
19
          sim$man_mi2 + sim$man_mi3 + sim$man_mi4 + sim$man_mi5 + sim$man_mi6 +
20
          sim$man mi7)
21
          sim$man bias2 = 1*((sim$man mi1 + sim$man mi2 + sim$man mi3 + sim$man mi4
22
          + sim$man mi5 + sim$man mi6 + sim$man mi7) > 3) - (sim$man mi1 +
23
          sim$man_mi2 + sim$man_mi3 + sim$man_mi4 + sim$man_mi5 + sim$man_mi6 +
24
          sim$man_mi7)
25
26
27
          sim$manic = (1- sim$man_ma1 * sim$man_ma2) * (sim$man_ma1 + sim$man_ma2)
28
          * sim$man ma3 * (sim$man mi1 + sim$man mi2 + sim$man mi3 + sim$man mi4 +
29
          sim$man mi5 + sim$man mi6 + sim$man mi7 + sim$man bias1) + (1 - (1 -
30
          sim$man_ma1 * sim$man_ma2) * (sim$man_ma1 + sim$man_ma2)) * sim$man_ma3 *
31
          (sim$man_mi1 + sim$man_mi2 + sim$man_mi3 + sim$man_mi4 + sim$man_mi5 +
32
          sim$man_mi6 + sim$man_mi7 + sim$man_bias2)
33
34
35
          sim$man_bias = sim$manic - (sim$man_ma1 + sim$man_ma2 + sim$man_ma3) -
36
          (sim$man_mi1 + sim$man_mi2 + sim$man_mi3 + sim$man_mi4 + sim$man_mi5 +
37
          sim$man_mi6 + sim$man_mi7 + sim$man_bias1) - (sim$man_bias2)
38
39
            ##end of generate data
40
41
            resu[, paste(collect, "_", c, sep = "")] = NA
42
43
              for(r in 1:nrow(resu)){
44
                #variable characteristics
45
                if(is.na(resu$variable[r]) == FALSE){
46
                  resu[r, paste0("derivedprevalence_", c, collapse = "")] =
47
          nrow(sim[which(sim[, resu$variable[r]] == 1),])/ssize
48
                  resu[r, paste0("mean_", c, collapse = "")] =
49
          mean(sim[,resu$variable[r]])
50
                  resu[r, paste0("max ", c, collapse = "")] =
51
          max(sim[,resu$variable[r]])
52
                  resu[r, paste0("min_", c, collapse = "")] =
53
          min(sim[,resu$variable[r]])
54
                }
55
                ##regression for the diagnosis
56
                if(is.na(resu$variable[r]) == FALSE & resu$variable[r] !=
57
          resu$outcome[r]){
58
                  eval(parse(text = paste0("templm = summary(lm(", resu$outcome[r],
59
          " ~ ", resu$variable[r], ", data = sim))", collpase = "")))
60
```

```
2
3
                  resu[r, paste0("coef_", c, collapse = "")] =
4
          templm$coefficients[resu$variable[r], "Estimate"]
5
                  resu[r, paste0("coefse_", c, collapse = "")] =
6
          templm$coefficients[resu$variable[r], "Std. Error"]
7
                  resu[r, paste0("p_", c, collapse = "")] =
8
          templm$coefficients[resu$variable[r], "Pr(>|t|)"]
9
          resu[r, paste0("intercept_", c, collapse = "")] =
templm$coefficients["(Intercept)", "Estimate"]
10
11
          resu[r, paste0("interceptp_", c, collapse = "")] =
templm$coefficients["(Intercept)", "Pr(>|t|)"]
12
13
                  resu[r, paste0("r2_", c, collapse = "")] = templm$r.squared
14
                }
15
                      ##regression for the suboutcome/domain variables
16
                if(is.na(resu$variable[r]) == FALSE & is.na(resu$suboutcome[r]) ==
17
          FALSE & resu$variable[r] != resu$outcome[r] & resu$variable[r] !=
18
          resu$suboutcome[r]){
19
                  eval(parse(text = paste0("templm = summary(lm(",
20
          resu$suboutcome[r], " ~ ", resu$variable[r], ", data = sim))", collpase =
21
          "")))
22
                  resu[r, paste0("subcoef_", c, collapse = "")] =
23
          templm$coefficients[resu$variable[r], "Estimate"]
24
                  resu[r, paste0("subcoefse_", c, collapse = "")] =
25
          templm$coefficients[resu$variable[r], "Std. Error"]
26
                  resu[r, paste0("subp_", c, collapse = "")] =
27
          templm$coefficients[resu$variable[r], "Pr(>|t|)"]
28
                  resu[r, paste0("subintercept ", c, collapse = "")] =
29
          30
                  resu[r, paste0("subinterceptp_", c, collapse = "")] =
31
          32
33
                }
34
35
36
                      if(r %in% as.character(1:100*50)){print(c("r:", r))}
37
              }#r = rows of the variable list
38
39
40
                  ##Approximation by own, bias or all variables
41
42
43
                    #ploting area_start: only the last simulation data set used for
44
          plotting
45
                    library(leaps)
46
                    #MDE
47
                    #own variables only
48
                    mdeown = NA
49
                    library(car)
50
                    sim.new = sim[,c("mde",
51
          names(summary((lm(as.formula(paste0("mde ~ ", paste0(names(sim))
52
          [grepl("mde_", names(sim)) == TRUE & grepl("bias", names(sim)) == FALSE],
          collapse = " + "), collapse = "")), data = sim)))$aliased)
53
54
          [summary((lm(as.formula(paste0("mde ~ ", paste0(names(sim)[grep1("mde_")
55
          names(sim)) == TRUE & grepl("bias", names(sim)) == FALSE], collapse = " +
56
          "), collapse = "")), data = sim)))$aliased == FALSE &
57
          58
          [grepl("mde_", names(sim)) == TRUE & grepl("bias", names(sim)) == FALSE],
59
          collapse = " + "), collapse = "")), data = sim)))$aliased) !=
60
          "(Intercept)"])]
```

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```
for(repe in 1:40){
                       tempvif = vif(lm(mde~., data = sim.new))
                       if(any(tempvif > 10)){
                      sim.new = sim.new[,which(names(sim.new) != names(tempvif)
          [which(tempvif == tempvif[order(-tempvif)][1])])]
                       ł
                     }
14
                     try(
                      (mdeown = regsubsets(mde~., data = sim.new, really.big=T,
          method = "forward", nvmax = ncol(sim.new))), silent = F
                     )
                    mdeownsummary = NA
20
                     if(any(is.na(mdeown)) == FALSE){
                      mdeownsummary = summary(mdeown)
22
                     }
                    mdeownsummary$adjr2
26
28
                     ##own and bias variables
                    mdebias = NA
30
                    mdebias = regsubsets(as.formula(paste0("mde ~ ",
32
          paste0(names(sim)[grepl("mde_", names(sim)) == TRUE & grepl("bias",
          names(sim)) == TRUE], collapse = " + "), collapse = "")), data = sim,
          nvmax = 100, really.big=T, method = "forward")
                    mdebiassummary = summary(mdebias)
36
                    mdebiassummary$adjr2
                     ##all variables
40
                    ###in case of collinearity
                    mdeall = NA
44
                    ##Deal with collinearity
                    library(car)
                     sim.new = sim[,c("mde", names(summary((lm(mde~., data = sim)))
          $aliased)[summary((lm(mde~., data = sim)))$aliased == FALSE &
          names(summary((lm(mde~., data = sim)))$aliased) != "(Intercept)"])]
                     for(repe in 1:40){
                       tempvif = vif(lm(mde~., data = sim.new))
                       if(any(tempvif > 10)){
                       sim.new = sim.new[,which(names(sim.new) != names(tempvif)
          [which(tempvif == tempvif[order(-tempvif)][1])])
                       }
                     }
58
59
                    ##Somehow there are problems in executing regsubsets even after
          removing collinear variables
```

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52 53

54

55

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58

```
try(
           (mdeall = regsubsets(mde~., data = sim.new, really.big=T,
method = "forward", nvmax = ncol(sim.new))), silent = F
         )
         mdeallsummary = NA
         if(any(is.na(mdeall)) == FALSE){
           mdeallsummary = summary(mdeall)
         ł
         # mdeallsummary$adjr2
         #DYS
         #dys
         #own variables only
         dysown = NA
               library(car)
         sim.new = sim[,c("dys",
[(grepl("dys_", names(sim)) == TRUE | grepl("mde_mi4", names(sim)) ==
TRUE | grepl("mde_mi6", names(sim)) == TRUE | grepl("mde_mi8",
names(sim)) == TRUE) & grepl("bias", names(sim)) == FALSE]), collapse = "
+ "), collapse = "")), data = sim)))$aliased)
[summary((lm(as.formula(paste0("dys ~ ", paste0(c(names(sim)
[(grepl("dys_", names(sim)) == TRUE | grepl("mde_mi4", names(sim)) ==
TRUE | grepl("mde_mi6", names(sim)) == TRUE | grepl("mde_mi8",
names(sim)) == TRUE) & grepl("bias", names(sim)) == FALSE]), collapse = "
+ "), collapse = "")), data = sim)))$aliased == FALSE &
names(summary((lm(as.formula(paste0("dys ~ ", paste0(c(names(sim)
[(grepl("dys_", names(sim)) == TRUE | grepl("mde_mi4", names(sim)) ==
TRUE | grep1("mde_mi6", names(sim)) == TRUE | grep1("mde_mi8",
names(sim)) == TRUE) & grepl("bias", names(sim)) == FALSE]), collapse = "
+ "), collapse = "")), data = sim)))$aliased) != "(Intercept)"])]
         for(repe in 1:40){
                     tempvif = vif(lm(dys~., data = sim.new))
             if(any(tempvif > 10)){
             sim.new = sim.new[,which(names(sim.new) != names(tempvif)
[which(tempvif == tempvif[order(-tempvif)][1])])
             }
         }
         ##Somehow there are problems in executing regsubsets even after
removing collinear variables
         try(
           (dysown = regsubsets(dys~., data = sim.new, really.big=T,
method = "forward", nvmax = 100)), silent = T
         )
         if(any(is.na(dysown)) == FALSE){
           dysownsummary = summary(dysown)
          }
         ##own and bias variables
         dysbias = NA
```

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```
dysbias = regsubsets(as.formula(paste0("dys ~ ",
          paste0(names(sim)[(grepl("dys_", names(sim)) == TRUE | grepl("mde_mi4",
          names(sim)) == TRUE | grepl("mde_mi6", names(sim)) == TRUE |
          grepl("mde_mi8", names(sim)) == TRUE) & grepl("bias", names(sim)) ==
          TRUE], collapse = " + "), collapse = "")), data = sim, nvmax = 100,
          really.big=T, method = "forward")
                    dysbiassummary = summary(dysbias)
10
                    dysbiassummary$adjr2
11
12
13
                    ##all variables
14
                    ###in case of collinearity
15
                    dysall = NA
16
                    library(car)
17
                    sim.new = sim[,c("dys", names(summary((lm(dys~., data = sim)))
18
          $aliased)[summary((lm(dys~., data = sim)))$aliased == FALSE &
19
          names(summary((lm(dys~., data = sim)))$aliased) != "(Intercept)"])]
20
21
                    for(repe in 1:40){
22
                                tempvif = vif(lm(dys~., data = sim.new))
23
                        if(any(tempvif > 10)){
24
                        sim.new = sim.new[,which(names(sim.new) != names(tempvif)
25
          [which(tempvif == tempvif[order(-tempvif)][1])])
26
                        }
27
                    }
28
                    ##Somehow there are problems in executing regsubsets even after
29
          removing collinear variables
30
                    try(
31
                      (dysall = regsubsets(dys~., data = sim.new, really.big=T,
32
          method = "forward", nvmax = 100)), silent = T
33
                    )
34
35
                    if(any(is.na(dysall)) == FALSE){
36
                      dysallsummary = summary(dysall)
37
                    }
38
                    # dysallsummary$adjr2
39
40
41
42
43
                    #manic
44
                    #own variables only
45
                    manown = NA
46
                              library(car)
47
                    sim.new = sim[,c("manic",
48
          49
          [grepl("man_", names(sim)) == TRUE & grepl("bias", names(sim)) == FALSE],
50
          collapse = " + "), collapse = "")), data = sim)))$aliased)
51
          [summary((lm(as.formula(paste0("manic ~ ", paste0(names(sim))
52
          [grepl("man_", names(sim)) == TRUE & grepl("bias", names(sim)) == FALSE],
          collapse = " + "), collapse = "")), data = sim)))$aliased == FALSE &
53
54
          names(summary((lm(as.formula(paste0("manic ~ ", paste0(names(sim)
55
          [grep1("man_", names(sim)) == TRUE & grep1("bias", names(sim)) == FALSE],
56
          collapse = " + "), collapse = "")), data = sim)))$aliased) !=
57
          "(Intercept)"])]
58
                    for(repe in 1:40){
59
                                tempvif = vif(lm(manic~., data = sim.new))
60
                        if(any(tempvif > 10)){
```

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```
sim.new = sim.new[,which(names(sim.new) != names(tempvif)
[which(tempvif == tempvif[order(-tempvif)][1])])
              }
          }
          try(
            (manown = regsubsets(manic~., data = sim.new, really.big=T,
method = "forward", nvmax = 100)), silent = T
          )
          manownsummary = NA
          if(any(is.na(manown)) == FALSE){
            manownsummary = summary(manown)
          }
          ##own and bias variables
          manbias = NA
          manbias = regsubsets(as.formula(paste0("manic ~ ",
paste0(names(sim)[grep1("man_", names(sim)) == TRUE & grep1("bias",
names(sim)) == TRUE], collapse = " + "), collapse = "")), data = sim,
nvmax = 100, really.big=T, method = "forward")
          manbiassummary = summary(manbias)
          manbiassummary$adjr2
          ##all variables
          ###in case of collinearity
          manall = NA
                    library(car)
          sim.new = sim[,c("manic", names(summary((lm(manic~., data =
sim)))$aliased)[summary((lm(manic~., data = sim)))$aliased == FALSE &
names(summary((lm(manic~., data = sim)))$aliased) != "(Intercept)"])]
          for(repe in 1:40){
                      tempvif = vif(lm(manic~., data = sim.new))
              if(any(tempvif > 10)){
              sim.new = sim.new[,which(names(sim.new) != names(tempvif)
[which(tempvif == tempvif[order(-tempvif)][1])]
          }
          ##Somehow there are problems in executing regsubsets even after
removing collinear variables
          try(
            (manall = regsubsets(manic~., data = sim.new, really.big=T,
method = "forward", nvmax = 100)), silent = T
          )
          manallsummary = NA
          if(any(is.na(manall)) == FALSE){
            manallsummary = summary(manall)
          }
  ##extract information from the outmat
       #MDE
          resu[which(resu$variable == "mde"), paste0("appbyownr2_", c,
collapse = "")] = mdeownsummary$adjr2[which.max(mdeownsummary$adjr2)]
          resu[which(resu$variable == "mde"), paste0("appbyownn_", c,
collapse = "")] = which.max(mdeownsummary$adjr2)
```

2	
3	resu[which(resu\$variab]e "mde")
4	college = []] = posto@(dimpercenter) mac /, pastco(appsyonnar_ , c,
5	[ubieb(mdeeuweeuwmeeuwfeutmet[ubieb_meeu(mdeeuweeuwmeeuwfedig2)] [ubu]]
6	[which(mdeownsummary\$outmat[which.max(mdeownsummary\$ad]r2),] == "*")],
7	collapse = ",")
/	
8	resu[which(resu\$variable == "mde"),
9	<pre>collapse = "")] = mdebiassummary\$adjr2[which.max(mdebiassummary\$adjr2)]</pre>
10	resu[which(resu\$variable == "mde"), paste0("appbybiasn ", c,
11	collapse = $""$] = which max(mdebiassummary\$adir2)
12	rosu[which(rosu\$variable "mde") pasto@("apphybiasvar " c
13	resu[which(resupvariable == mue), pasted(appbyblasvar_ , c,
14	collapse = "")] = pasteo(dimnames(mdeblassummary\$outmat)[[2]]
15	[which(mdeblassummary\$outmat[which.max(mdeblassummary\$ad]r2),] == "*")],
15	collapse = ",")
16	
17	if(any(is.na(mdeall)) == FALSE){
18	resu[which(resu\$variable == "mde"),
19	<pre>c, collapse = "")] = mdeallsummarv\$adir2[which.max(mdeallsummarv\$adir2)]</pre>
20	resu[which(resu\$variable == "mde") paste@("apphyallp " c
21	collapso - "")] - which max(mdoallsummary\$adir2)
22	rocu[wbich(rocutevariable - mdell) = material (apphysical) + materia
23	resulwhich(resupvariable == "mue"), pasteo("appbyalivar_",
23	c, collapse = "")] = paste0(dimnames(mdeallsummary\$outmat)[[2]]
24	[which(mdeallsummary\$outmat[which.max(mdeallsummary\$adjr2),] == "*")],
25	collapse = ",")
26	
27	}
28	
29	
30	#DYS
31	resu[which(resu\$variable == "dvs")naste0("apphyowpr2 "
32	collapse = "")] = dysownsummary&adir2[which max(dysownsummary&adir2)]
33	reculude (reculution) = uysownsummarysaujiz[which:max(uysownsummarysaujiz)]
34	resu[which(resu\$variable == "dys"), paste0("appbyowhn_", C,
25	collapse = "")] = which.max(dysownsummary\$ad]r2)
32	resu[which(resu\$variable == "dys"), paste0("appbyownvar_", c,
30	collapse = "")] = paste0(dimnames(dysownsummary\$outmat)[[2]]
3/	[which(dysownsummary\$outmat[which.max(dysownsummary\$adjr2),] == "*")],
38	collapse = ",")
39	
40	resu[which(resu\$variable == "dvs"), paste0("appbybiasr2 ", c,
41	collapse = "")] = $dysbiassummary$ adir2[which.max(dysbiassummary\$adir2)]
42	resu[which(resu\$variable == "dvs") naste0("annbybiasn " c
43	collarse = "")] = which max(dyshiassummary\$adir2)
44	$rocu[which(rocu^{(u)}) = $
45	resulwhich(resupvariable == "uys"), pasteb("appbyblasvar_", C,
	corrapse = "")] = pastev(armnames(aysplassummary\$outmat)[[2]]
то 47	<pre>[wnicn(dysblassummary\$outmat[which.max(dysblassummary\$ad]r2),] == "*")],</pre>
4/	collapse = ",")
48	
49	if(any(is.na(dysall)) == FALSE){
50	resu[which(resu\$variable == "dys"),
51	collapse = "")] = dysallsummary\$adjr2[which.max(dysallsummary\$adjr2)]
52	resu[which(resu\$variable == "dvs"), paste0("apphyalln " c
53	collarse = "")] = which max(dysallsummary\$adir2)
54	$rocu[which(rocu^{(u)}) = $
55	resulwhith(resupvariable uys /, pasteb("appbyarivar_", C,
56	<pre>corrapse = "")] = pastev(armnames(aysarrsummary\$Outmat)[[2]]</pre>
50	<pre>[wnicn(dysallsummary\$outmat[wnicn.max(dysallsummary\$ad]r2),] == "*")],</pre>
57	collapse = ",")
58	}
59	
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```
#MANIC
          resu[which(resu$variable == "manic"), paste0("appbyownr2_", c,
collapse = "")] = manownsummary$adjr2[which.max(manownsummary$adjr2)]
         resu[which(resu$variable == "manic"), paste0("appbyownn_", c,
collapse = "")] = which.max(manownsummary$adjr2)
          resu[which(resu$variable == "manic"), paste0("appbyownvar_", c,
collapse = "")] = paste0(dimnames(manownsummary$outmat)[[2]]
[which(manownsummary$outmat[which.max(manownsummary$adjr2),] == "*")],
collapse = ",")
         resu[which(resu$variable == "manic"), paste0("appbybiasr2_", c,
collapse = "")] = manbiassummary$adjr2[which.max(manbiassummary$adjr2)]
         resu[which(resu$variable == "manic"), paste0("appbybiasn_", c,
collapse = "")] = which.max(manbiassummary$adjr2)
          resu[which(resu$variable == "manic"), paste0("appbybiasvar_",
c, collapse = "")] = paste0(dimnames(manbiassummary$outmat)[[2]]
[which(manbiassummary$outmat[which.max(manbiassummary$adjr2),] == "*")],
collapse = ",")
          if(any(is.na(manall)) == FALSE){
            resu[which(resu$variable == "manic"), paste0("appbyallr2_",
c, collapse = "")] = manallsummary$adjr2[which.max(manallsummary$adjr2)]
            resu[which(resu$variable == "manic"), paste0("appbyalln_", c,
collapse = "")] = which.max(manallsummary$adjr2)
            resu[which(resu$variable == "manic"), paste0("appbyallvar ",
c, collapse = "")] = paste0(dimnames(manallsummary$outmat)[[2]]
[which(manallsummary$outmat[which.max(manallsummary$adjr2),] == "*")],
collapse = ",")
          }
            print(c("c:", c))
            print(c("cor:", rho[rh]))
            print(c("Prevalence: ", prevalence[preval]))
    }#c
    ##adding summary statistics to the result data frame
resu[, paste(collect, "_mean", sep = "")] = NA
resu[, paste(collect, "_sd", sep = "")] = NA
resu[, paste(collect, "_se", sep = "")] = NA
resu[, paste(collect, "_95up", sep = "")] = NA
resu[, paste(collect, "_951o", sep = "")] = NA
resu[, paste(collect, "_rangeup", sep = "")] = NA
resu[, paste(collect, "_rangelo", sep = "")] = NA
for(co in 1:length(collect)){
  for(r in 1:nrow(resu)){
    if((collect[co] %in% c("appbyownvar", "appbybiasvar", "appbyallvar"))
== FALSE){
          resu[r,paste0(collect[co], "_mean", collapse = "")] =
mean(unlist(resu[r, paste(collect[co], "_", 1:times, sep = "")])[which(!
is.na(unlist(resu[r, paste(collect[co], "_", 1:times, sep = "")])))])
```

```
resu[r,paste0(collect[co], "_sd", collapse = "")] = sd(unlist(resu[r,
paste(collect[co], "_", 1:times, sep = "")])[which(!is.na(unlist(resu[r,
paste(collect[co], "_", 1:times, sep = "")])))])
     resu[r,paste0(collect[co], "_se", collapse = "")] = sd(unlist(resu[r,
paste(collect[co], "_", 1:times, sep = "")])[which(!is.na(unlist(resu[r,
paste(collect[co], "_", 1:times, sep = "")])))])/(times^0.5)
     #95% CIs
     resu[r,paste0(collect[co], "_95up", collapse = "")] =
resu[r,paste0(collect[co], "_mean", collapse = "")] +
1.96*resu[r,paste0(collect[co], "_se", collapse = "")]
     resu[r,paste0(collect[co], "_951o", collapse = "")] =
resu[r,paste0(collect[co], "_mean", collapse = "")] -
1.96*resu[r,paste0(collect[co], "_se", collapse = "")]
     #range
          resu[r,paste0(collect[co], "_rangelo", collapse = "")] =
min(resu[r,paste(collect[co], "_", 1:times, sep = "")])
          resu[r,paste0(collect[co], "_rangeup", collapse = "")] =
max(resu[r,paste(collect[co], "_", 1:times, sep = "")])
  }#r
     ##Add information about the aliased variables
     ##save in another data set
     eval(parse(text = paste0("resu_cor", rho[rh], "_preval",
prevalence[preval], " = resu", collapse = "")))
     }
#export results
write.csv(cbind(resu[,c("definition", "variable", "mean_mean",
"mean_95up", "mean_95lo", "max_rangeup",
"min_rangelo", "mean_/910 , "max_langedp ,
"min_rangelo", "derivedprevalence_mean", "derivedprevalence_95up",
"derivedprevalence_95lo", "coef_mean", "coef_95up", "coef_95lo",
"p_mean", "p_95up", "p_95lo", "r2_mean", "r2_95up",
"r2_95lo", "subcoef_mean", "subcoef_95up", "subcoef_95lo",
"subp_mean", "subp_95up", "subp_95lo", "subr2_mean", "subr2_95up",
"subr2_95lo", "appbyownr2_mean", "appbyownr2_95up", "appbyownr2_95lo",
"appbyownn_mean", "appbyownn_95up", "appbyownn_95lo", "appbybiasr2_mean",
"appbybiasr2_95up", "appbybiasr2_95lo", "appbybiasn_mean",
"appbybiasn_95up", "appbybiasn_95lo", "appbyallr2_mean",
"appbyallr2_95up", "appbyallr2_95lo", "appbyalln_mean", "appbyalln_95up",
"appbyalln 951o"
)], resu), file = paste0("simulation results_cor", rho[rh], "_preval",
prevalence[preval], ".csv"))
  }#co
```

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print(c("cor:", rho[rh]))

}#rho

print(c("Prevalence: ", prevalence[preval]))

#store data .unce[pre print(c("Prevalence: ", prevalence[preval])) }#prevalence • • •



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