

Counting unique symptom profiles of Major Depressive Disorder and Major Depressive Disorder with melancholic features

In the following document, we calculate the number of unique symptom profiles for Major Depressive Disorder (MDD) and MDD with the melancholic specifier (MDDm), according to the DSM-5. We count both profiles twice. First, we count the profiles according to the strict wording of the DSM; this means that criteria such as "insomnia or hypersomnia" are counted as one symptom. Second, we count the profiles a second time, this time differentiating between subsymptoms.

We will refer to the 9 MDD symptoms listed in the DSM-5 as D1-D9 instead of A1-A9 to avoid confusion with the melancholic symptoms that have the same abbreviations. We refer to the MDDm symptoms as A1-A2 and B1-B6, in the same way the DSM-5 does.

1 Strict counting: only necessary symptom splits

In this section we will count the MDD and MDDm symptom profiles by making use of the symptoms as they are defined in the DSM-5. However, in order to do the MDDm counting properly, we are obliged to split up 3 of the 9 MDD symptoms in three pairs of subsymptoms since some of the MDDm symptoms are exactly these MDD subsymptoms. For example, the MDDm symptom B5 (weight loss) is part of the MDD symptom D3 (weight loss or weight gain). In the first part of this section we will count the number of symptom profiles corresponding to MDD. In the second part we will do this counting again but now by making use of the three splits that are necessary for a proper counting of the MDDm symptom profiles. This latter counting will be discussed in the last part of this section.

1.1 Number of MDD symptom profiles: no symptom splits

We first count the number of MDD symptom profiles without splitting any of the symptoms D1 to D9.

1. If both D1 and D2 are present, at least 3 out of the 7 symptoms D3 to D9 have to be present in order to qualify for MDD. Hence, there are

$$\binom{7}{3} + \binom{7}{4} + \binom{7}{5} + \binom{7}{6} + \binom{7}{7} = 99 \tag{1.1}$$

MDD symptom profiles that have both symptoms D1 and D2 present.

2. If D1 is present and D2 is not, at least 4 out of the 7 symptoms D3 to D9 have to be present in order to qualify for MDD. Hence, there are 64 MDD symptom profiles that have D1 present and D2 not.
3. If D2 is present and D1 not, we find analogously as in the previous point that there are 64 corresponding MDD symptom profiles.

Hence in total there are $99 + 64 + 64 = \mathbf{227}$ MDD symptom profiles.

1.2 Number of MDD symptom profiles: necessary symptom splits for proper MDDm counting

If one qualifies for MDD, in order to qualify for MDDm A1 or A2 need to be present together with at least 3 out of the 6 symptoms B1 to B6. However, since A1 (loss of pleasure) is part of D2 (loss of interest or loss of pleasure), since B3 (early-morning awakening) is part of D4 (insomnia or hypersomnia) and since B5 (anorexia or weight loss) is part of D3 (weight loss or weight gain) we have to split up symptoms D2, D3 and D4 in order to do the counting properly. We will split up these symptoms as follows:

- D2 will be split up in D2(1) (loss of interest) and D2(2) (loss of pleasure). Both symptoms can be present simultaneously.
- D3 will be split up in D3(1) (weight loss or decreased appetite) and D3(2) (weight gain or increased appetite). Both symptoms cannot be present simultaneously¹.
- D4 will be split up into D4(1) (insomnia) and D4(2) (hypersomnia). Both symptoms cannot be present simultaneously².

Let us first recount the number of MDD symptom profiles by making use of these splitted symptoms. Depending on whether D1 and/or D2 are present, at least 3 or 4 out of the 7 symptoms D3 to D9 have to be present in order to qualify for MDD. However, both D3 and D4 are splitted into two subsymptoms that cannot be present simultaneously. This complicates the counting a little bit. Let us count the number of possible ways we can choose 3 to 7 symptoms from the D3 to D9 list. To do this we divide the symptoms in two groups depending on whether or not they are split up into subsymptoms that cannot be mutually present. The two groups are (D3, D4) and (D5, D6, D7, D8, D9).

¹We are very conservative in our split: we consider weight loss and decreased appetite to be one and the same symptom and we also consider weight gain and increased appetite to be one and the same symptom. Moreover, we assume that both D3(1) and D3(2) cannot be present simultaneously.

²Again, we are being very conservative here since it is very well possible that a person exhibits insomnia as well as hypersomnia over the course of 2 weeks. Moreover, we take symptom B3 (early morning awakening) to be equivalent to D4(1) (insomnia) while strictly speaking it is only a part of it.

- 3 symptoms:

$$4 \times \binom{5}{1} + 4 \times \binom{5}{2} + \binom{5}{3} = 70, \quad (1.2)$$

where the first term corresponds to choosing two symptoms from group 1 and one from group 2, the second term corresponds to choosing one symptom from group 1 and two from group 2 and the third term corresponds to choosing zero symptoms from group 1 and three from group 2.

- 4 symptoms:

$$4 \times \binom{5}{2} + 4 \times \binom{5}{3} + \binom{5}{4} = 85, \quad (1.3)$$

in an analogous way as described above.

- 5 symptoms:

$$4 \times \binom{5}{3} + 4 \times \binom{5}{4} + \binom{5}{5} = 61, \quad (1.4)$$

in an analogous way as described above.

- 6 symptoms:

$$4 \times \binom{5}{4} + 4 \times \binom{5}{5} = 24, \quad (1.5)$$

in an analogous way as described above.

- 7 symptoms:

$$4 \times \binom{5}{5} = 4, \quad (1.6)$$

in an analogous way as described above.

Let us now do the counting for MDD.

1. If both D1 and D2 are present (and this can happen in three different ways: D1 & D2(1), D1 & D2(2), D1 & D2(1) & D2(2)), at least 3 out of the 7 symptoms D3 to D9 have to be present in order to qualify for MDD. Hence, there are

$$3 \times \{70 + 85 + 61 + 24 + 4\} = 3 \times 244 = 732 \quad (1.7)$$

MDD symptom profiles that have both D1 as well as D2 present.

2. If D1 is present and D2 is not, at least 4 out of the 7 symptoms D3 to D9 have to be present in order to qualify for MDD. Hence, there are

$$85 + 61 + 24 + 4 = 174 \quad (1.8)$$

MDD symptom profiles that have only D1 present.

3. If D2 is present and D1 is not (and this can again happen in 3 different ways: D2(1), D2(2), D2(1) & D2(2)), we find analogously as in the previous point that there are $3 \times 174 = 522$ corresponding MDD symptom profiles.

Hence, after the conservative splitting of symptoms D2, D3 and D4 there are $732+174+522 = 1428$ MDD symptom profiles.

1.3 Number of MDDm symptom profiles

Since symptoms B3, B4 and B5 are, respectively, equal to symptoms D4(1), D5 and D3(1), it proves to be useful to split up the 244 D1 *and* D2 MDD symptom profiles and the 174 D1 *or* D2 symptom profiles as:

$$244 = 42 + 57 + 26 + 26 + 31 + 31 + 15 + 16, \quad (1.9)$$

$$174 = 22 + 42 + 16 + 16 + 26 + 26 + 11 + 15, \quad (1.10)$$

where each of the eight numbers on the right hand sides corresponds, respectively, to symptom profiles that do not contain symptoms D3(1), D4(1) and D5, symptom profiles that do not contain symptoms D3(1) and D4(1) but do contain symptom D5, symptom profiles that do not contain symptoms D3(1) and D5 but do contain D4(1), symptom profiles that do not contain symptoms D4(1) and D5 but do contain D3(1), symptom profiles that do not contain symptom D3(1) but do contain symptoms D4(1) and D5, symptom profiles that do not contain symptom D4(1) but do contain symptoms D3(1) and D5, symptom profiles that do not contain symptom D5 but do contain symptoms D3(1) and D4(1) and symptom profiles that contain symptoms D3(1), D4(1) and D5.

Now, let us count the symptom profiles that correspond to MDDm. Apart from the fact that one should qualify for MDD, either symptom D2(2) has to be present (which is the same as symptom A1) or symptom A2, together with at least 3 out of the 6 symptoms B1 to B6. The latter requirement corresponds to

$$\binom{6}{3} + \binom{6}{4} + \binom{6}{5} + \binom{6}{6} = 42 \quad (1.11)$$

possibilities. Since symptoms B3, B4 and B5 are, respectively, equal to symptoms D4(1), D5 and D3(1), we split up this number as

$$42 = 1 + 4 + 4 + 4 + 7 + 7 + 7 + 8, \quad (1.12)$$

exactly as we did in equations (1.9) and (1.10).

All this amounts to the following final symptom count. We consider four cases: MDD with symptoms D1 and D2(2) present (and eventually D2(1)), MDD with symptom D2(2) present (and eventually D2(1)) but not D1, MDD with symptom D1 present (and eventually D2(1)) but not D2(2) and MDD with symptom D2(1) present but not D1 and D2(2). In the first two cases, to qualify for MDDm symptom A2 is optional, whereas in the last two cases it is required.

- MDD with symptoms D1 and D2(2) present (and eventually D2(1)): symptom A2 is optional and we need at least 3 out of the 6 symptoms B1 to B6. From (1.9) and (1.12) we find that there are

$$4 \times \left(42 \times 1 + 57 \times 4 + 26 \times 4 + 26 \times 4 + 31 \times 7 + 31 \times 7 + 15 \times 7 + 16 \times 8 \right) = 4580 \quad (1.13)$$

corresponding symptom profiles. The factor of 4 in front corresponds to the fact that symptoms D2(1) and A2 are optional.

- MDD with symptom D2(2) present (and eventually D2(1)) and not D1: symptom A2 is optional and we need at least 3 out of the 6 symptoms B1 to B6. From (1.10) and (1.12) we find that there are

$$4 \times \left(22 \times 1 + 42 \times 4 + 16 \times 4 + 16 \times 4 + 26 \times 7 + 26 \times 7 + 11 \times 7 + 15 \times 8 \right) = 3516 \quad (1.14)$$

corresponding symptom profiles. The factor of 4 in front corresponds to the fact that symptoms D2(1) and A2 are optional.

- MDD with symptom D1 present (and eventually D2(1)) and not D2(2): symptom A2 is required and we need at least 3 out of the 6 symptoms B1 to B6. From (1.9), (1.10) and (1.12) we find that there are

$$\begin{aligned} & \left(42 \times 1 + 57 \times 4 + 26 \times 4 + 26 \times 4 + 31 \times 7 + 31 \times 7 + 15 \times 7 + 16 \times 8 \right) + \\ & \left(22 \times 1 + 42 \times 4 + 16 \times 4 + 16 \times 4 + 26 \times 7 + 26 \times 7 + 11 \times 7 + 15 \times 8 \right) \\ & = 2024 \end{aligned} \quad (1.15)$$

corresponding symptom profiles. Where the two lines of the equation correspond to whether or not symptom D2(1) is present.

- MDD with symptom D2(1) present and not D1 and D2(2): symptom A2 is required and we need at least 3 out of the 6 symptoms B1 to B6. From (1.10) and (1.12) we find that there are

$$\left(22 \times 1 + 42 \times 4 + 16 \times 4 + 16 \times 4 + 26 \times 7 + 26 \times 7 + 11 \times 7 + 15 \times 8 \right) = 879 \quad (1.16)$$

corresponding symptom profiles.

Hence, in total, there are $4580+3516+2024+879=10999$ MDDm symptom profiles.

2 Split symptom counting

In this second calculation for MDD and MDDm unique symptom profiles, we differentiate between subsymptoms such as “insomnia or hypersomnia”. However, we perform a the differentiation based on a number of conservative assumptions. While opposite subsymptoms (e.g., “psychomotor agitation or psychomotor retardation”) and disparate subsymptoms (e.g., “feeling worthless or guilty”) are counted as separate symptoms, we do not count others such as “feeling tired or without energy” separately. Likewise, we assume that opposite subsymptoms cannot both be present (e.g, “insomnia and hypersomnia”), although it is certainly possible to encounter both insomnia and hypersomnia in the last 2 weeks, while disparate subsymptoms can be (“feeling guilty and worthless”). From now on we will, for ease of presentation, refer to symptoms D1-D9, A1, A2 and B1-B6 as symptom categories and to subsymptoms as just symptoms.

2.1 Number of MDD symptom profiles

We first count the number of unique symptom profiles that correspond to MDD. According to our conservative assumptions, we will split up the symptom categories in the following way:

- symptom category D1: no split.
- symptom category D2: split into 2 different symptoms *that can both be present*: D2(1) (less interested) and D2(2) (less able to enjoy things).
- symptom category D3: split into 2 different symptoms *that cannot both be present*: D3(1) (appetite decrease/weight loss) and D3(2) (appetite increase/weight gain).
- symptom category D4: split into 2 different symptoms *that cannot both be present*: D4(1) (insomnia) and D4(2) (hypersomnia).
- symptom category D5: split into 2 different symptoms *that cannot both be present*: D5(1) (slow behavior) and D5(2) (restless behavior).
- symptom category D6: no split.
- symptom category D7: split into 2 different symptoms *that can both be present*: D7(1) (feeling worthless) and D7(2) (feeling guilty).
- symptom category D8: split into 2 different symptoms *that can both be present*: D8(1) (concentration problems) and D8(2) (hard to make decisions).
- symptom category D9: no split.

First of all, let us look at symptom categories D3 to D9 in a bit more detail. Depending on the presence of symptom categories D1 and D2, we need at least 3 or at least 4 symptoms *in different categories* D3 to D9 in order for a symptom profile to qualify as an MDD one.

For both the case in which at least 3 categories need to be represented (case 1) as the case in which at least 4 categories need to be represented (case 2), let us count the number of possible ways we can choose 3 to 9 (which is the maximum amount) symptoms from the D3 to D9 list. To do this we divide the symptom categories in two groups depending on whether or not they contain symptoms that cannot be mutually present. The two groups are (D3, D4 and D5) and (D6,D7,D8,D9).

- **3 symptoms**

case 1:

$$8 \times 1 + 12 \times \binom{6}{1} + 6 \times \binom{6}{2} + 1 \times \binom{6}{3} - 6 \times 2 - 1 \times 8 = 170, \quad (2.1)$$

where the first term corresponds to choosing three symptoms from group 1 and zero from group 2, the second term corresponds to choosing two symptoms from group 1 and one from group 2, the third term corresponds to choosing one symptom from group 1 and two from group 2, the fourth term corresponds to choosing zero symptoms from group 1 and three from group 3 and the last two terms subtract the symptom patterns that have two items in the same category and hence do not qualify as an MDD symptom pattern.

case 2: In the case that we need at least 4 different symptom categories, symptom profiles with only 3 symptoms do not qualify for MDD.

- **4 symptoms**

case 1:

$$8 \times \binom{6}{1} + 12 \times \binom{6}{2} + 6 \times \binom{6}{3} + 1 \times \binom{6}{4} - 1 = 362. \quad (2.2)$$

in an analogous way as described above.

case 2: In the case that we need at least 4 different symptom categories, the counting changes as follows

$$8 \times \binom{6}{1} + 12 \times \binom{6}{2} + 6 \times \binom{6}{3} + 1 \times \binom{6}{4} - 12 \times 2 - 6 \times 8 - 11 = 280. \quad (2.3)$$

- **5 symptoms**

case 1:

$$8 \times \binom{6}{2} + 12 \times \binom{6}{3} + 6 \times \binom{6}{4} + 1 \times \binom{6}{5} = 456. \quad (2.4)$$

in an analogous way as described above.

case 2: In the case that we need at least 4 different symptom categories, the counting changes as follows

$$8 \times \binom{6}{2} + 12 \times \binom{6}{3} + 6 \times \binom{6}{4} + 1 \times \binom{6}{5} - 6 - 2 = 448. \quad (2.5)$$

- **6 symptoms**

case 1:

$$8 \times \binom{6}{3} + 12 \times \binom{6}{4} + 6 \times \binom{6}{5} + 1 \times \binom{6}{6} = 377. \quad (2.6)$$

in an analogous way as described above.

case 2: The same in the case that we need at least 4 different symptom categories.

- **7 symptoms**

case 1:

$$8 \times \binom{6}{4} + 12 \times \binom{6}{5} + 6 \times \binom{6}{6} = 198. \quad (2.7)$$

in an analogous way as described above.

case 2: The same in the case that we need at least 4 different symptom categories.

- **8 symptoms**

case 1:

$$8 \times \binom{6}{5} + 12 \times \binom{6}{6} = 60. \quad (2.8)$$

in an analogous way as described above.

case 2: The same in the case that we need at least 4 different symptom categories.

- **9 symptoms:**

case 1:

$$8 \times \binom{6}{6} = 8. \quad (2.9)$$

in an analogous way as described above.

case 2: The same in the case that we need at least 4 different symptom categories.

Let us now do the counting for MDD.

1. If both categories D1 and D2 are represented, and this can happen in 3 different ways (D1 & D2(1) & D2(2), D1 & D2(1), D1 & D2(2)), at least 3 out of the 7 symptom *categories* D3 to D9 have to be represented in order to qualify for MDD. Hence, there are

$$3 \times \{170 + 362 + 456 + 377 + 198 + 60 + 8\} = 3 \times 1631 = 4893 \quad (2.10)$$

corresponding MDD symptom profiles.

2. If D1 is represented and category D2 is not, at least 4 out of the 7 symptom *categories* D3 to D9 have to be present in order to qualify for MDD (and we have to use the counts indicated in red above). Hence, there are

$$280 + 448 + 377 + 198 + 60 + 8 = 1371 \quad (2.11)$$

corresponding MDD symptom profiles.

3. If category D2 is represented and D1 is not, and this can happen in 3 different ways (D2(1) & D2(2), D2(1), D2(2)), we find analogously as in the previous point that there are $3 \times 1371 = 4113$ corresponding MDD symptom profiles.

Hence in total there are $4893 + 1371 + 4113 = \mathbf{10377}$ MDD symptom profiles.

2.2 Number of MDDm symptom profiles

To count the number of symptom profiles that correspond to MDDm it proves to be useful to split up the 1631 D1 *and* D2 MDD symptom profiles and the 1371 D1 *or* D2 symptom profiles as:

$$1631 = 206 + 490 + 118 + 118 + 254 + 254 + 63 + 128, \quad (2.12)$$

$$1371 = 130 + 412 + 88 + 88 + 236 + 236 + 55 + 126, \quad (2.13)$$

where each of the eight numbers on the right hand sides corresponds, respectively, to symptom profiles that do not contain symptoms D3(1), D4(1) and D5, symptom profiles that do not contain symptoms D3(1) and D4(1) but do contain symptom D5, symptom profiles that do not contain symptoms D3(1) and D5 but do contain D4(1), symptom profiles that do not contain symptoms D4(1) and D5 but do contain D3(1), symptom profiles that do not contain symptom D3(1) but do contain symptoms D4(1) and D5, symptom profiles that do not contain symptom D4(1) but do contain symptoms D3(1) and D5, symptom profiles that do not contain symptom D5 but do contain symptoms D3(1) and D4(1) and symptom profiles that contain symptoms D3(1), D4(1) and D5.

Now, let us count the symptom profiles that correspond to MDDm. Apart from the fact that one should qualify for MDD, either symptom D2(2) has to be present (which is the same as symptom A1) or symptom A2, and at least 3 out of the 6 symptom categories B1 to B6 need to be represented. These categories are defined by performing the following splits:

- symptom category B1: no split.
- symptom category B2: no split.
- symptom category B3: this corresponds to symptom D4(1).
- symptom category B4: this corresponds to symptom D3(1).
- symptom category B5: this corresponds to category D5.
- symptom category B6: split into 2 different symptoms *that can both be present*: B6(1) (excessive guilt) and B6(2) (out of proportion).

Then, the requirement that at least 3 out of the 6 symptom categories B1 to B6 have to be present corresponds to 150 possibilities (this number is computed analogously as the numbers in equation (2.10) or (2.11)). Analogous to equations (2.12) and (2.13) we split up this number as

$$150 = 3 + 20 + 10 + 10 + 30 + 30 + 15 + 32. \quad (2.14)$$

All this amounts to the following final symptom count. We consider four cases: MDD with symptoms D1 and D2(2) present (and eventually D2(1)), MDD with symptom D2(2) present (and eventually D2(1)) but not D1, MDD with symptom D1 present (and eventually D2(1)) but not D2(2) and MDD with symptom D2(1) present but not D1 and D2(2). In the first two cases, to qualify for MDDm symptom A2 is optional, whereas in the last two cases it is required.

- MDD with symptoms D1 and D2(2) present (and eventually D2(1)): symptom A2 is optional and we need at least 3 out of the 6 symptom categories B1 to B6. From (2.12) and (2.14) we find that there are

$$4 \times \left(206 \times 3 + 490 \times 20 + 118 \times 10 + 118 \times 10 + 254 \times 30 + 254 \times 30 + 63 \times 15 + 128 \times 32 \right) = 132236 \quad (2.15)$$

corresponding symptom profiles. The factor of 4 in front corresponds to the fact that symptoms D2(1) and A2 are optional.

- MDD with symptom D2(2) present (and eventually D2(1)) and not D1: symptom A2 is optional and we need at least 3 out of the 6 symptoms B1 to B6. From (2.13) and (2.14) we find that there are

$$4 \times \left(130 \times 3 + 412 \times 20 + 88 \times 10 + 88 \times 10 + 236 \times 30 + 236 \times 30 + 55 \times 15 + 126 \times 32 \right) = 117628 \quad (2.16)$$

corresponding symptom profiles. The factor of 4 in front corresponds to the fact that symptoms D2(1) and A2 are optional.

- MDD with symptom D1 present (and eventually D2(1)) and not D2(2): symptom A2 is required and we need at least 3 out of the 6 symptoms B1 to B6. From (2.12), (2.13) and (2.14) we find that there are

$$\left(206 \times 3 + 490 \times 20 + 118 \times 10 + 118 \times 10 + 254 \times 30 + 254 \times 30 + 63 \times 15 + 128 \times 32 \right) + \left(130 \times 3 + 412 \times 20 + 88 \times 10 + 88 \times 10 + 236 \times 30 + 236 \times 30 + 55 \times 15 + 126 \times 32 \right) = 62466 \quad (2.17)$$

corresponding symptom profiles. Where the two sums between brackets correspond to whether or not symptom D2(1) is present.

- MDD with symptom D2(1) present and not D1 and D2(2): symptom A2 is required and we need at least 3 out of the 6 symptoms B1 to B6. From (2.13) and (2.14) we find that there are

$$130 \times 3 + 412 \times 20 + 88 \times 10 + 88 \times 10 + 236 \times 30 + 236 \times 30 + 55 \times 15 + 126 \times 32 = 29407 \quad (2.18)$$

corresponding symptom profiles.

Hence, in total, there are $132236+117628+62466+29407=$ **341737** MDDm symptom profiles.