

1 Running Head: AETIOLOGICAL ARCHITECTURE OF DEPRESSIVE SYMPTOMS

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3 **Phenotypic and aetiological architecture of depressive symptoms in a Japanese twin**  
4 **sample**

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**Abstract**

1  
2 **Background:** The phenotypic and aetiological architecture of depression symptomatology  
3 has been mostly studied in Western samples. In this study, we conducted a genetically  
4 informed factor analysis to elucidate both the phenotypic and aetiological architectures of  
5 self-reported depression among a Japanese adult twin sample. **Methods:** Depressive  
6 symptoms assessed by Zung's Self-rating Depression Scale were self-rated by 425 twin  
7 pairs (301 monozygotic and 124 dizygotic twin pairs) in a community sample in Japan.  
8 **Results:** An exploratory factor analysis extracted three symptom domains representing  
9 cognitive, affective, and somatic symptomatology. A confirmatory factor analysis  
10 demonstrated that a bi-factor solution fitted better than the alternative solutions, implying  
11 that depression may be defined as a combination of a single general construct and three  
12 factors specific to each of the three symptom domains. A multivariate genetic analysis with  
13 the bi-factor solution showed that the general factor was substantially heritable (47%), and  
14 that only the affective symptom domain was significantly heritable (29%) among the three  
15 specific factors, their remaining variance being explained by non-shared environmental  
16 influences. **Conclusions:** Depression symptomatology appears to be adequately captured  
17 by a substantially heritable general factor. The heritability of this factor (47%) in a  
18 Japanese adult sample is in line with commonly reported heritability estimates for  
19 depression. The three specific factors – cognitive, affective, and somatic – are mostly  
20 explained by non-shared environmental factors, which include measurement error. The

1 extent to which these specific factors are uniquely associated with correlates of depression

2 when the general factor is accounted for should be investigated in future studies.

3

4 **Keywords:** depression, heritability, behavioural genetics, twin study, bi-factor model

1 **Phenotypic and aetiological architecture of depressive symptoms in a Japanese twin**  
2 **sample**

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4 According to the report by the World Health Organisation (2017), more than 300  
5 million people suffer from depression across the globe and depression is ranked in the  
6 top-ten causes of early death. In Japan, the lifetime prevalence of depression is comprised  
7 between 3% and 7% (i.e. major depressive disorder as defined by the DSM-5 criteria;  
8 American Psychiatric Association, 2013, Kawakami, 2007, Kessler & Bromet, 2013).  
9 Although the prevalence is somewhat lower in Japan than in Western countries (Kessler &  
10 Bromet, 2013), major depression still constitutes a rather common disorder compared with  
11 other psychiatric disorders.

12 Accurately assessing depressive symptoms within and across populations constitutes  
13 an essential first step before elucidating the aetiology of depression. However, differences  
14 in the phenotypic architecture of dimensional measures of depression are found across  
15 populations. The typical three factor structure (i.e. cognitive, affective, and somatic  
16 symptom domains) of Zung's (1965) Self-rating Depression Scale or SDS is sometimes  
17 found to differ across ethnically different samples. For example, four factors were found in  
18 Spanish and US samples (Passik et al., 2000; Romera et al., 2008). Within the Spanish  
19 sample the symptom factors reflected core depressive, cognitive, anxiety, and somatic  
20 factors; whereas in the US sample, the factors were slightly different, reflecting cognitive

1 symptoms, manifested by depressed mood, somatic non-eating, and somatic eating  
2 behaviour. Meanwhile, fewer factors tend to be extracted within Asian samples. For  
3 example, an early study of ethnically Chinese people drawn from community-based clinical  
4 and non-clinical samples from Hong Kong found two factors described as: depression with  
5 somatic complaints and negative view of life (Lee et al., 1994). A study of the Japanese  
6 general population found two factors: depressed affect and emptiness (Chida et al., 2004).  
7 However, three studies in Japanese undergraduates or mothers around birth have replicated  
8 the original three factors: cognitive, affective, and somatic symptoms (Kitamura et al.,  
9 2004; Sakamoto et al., 1998; Sugawara et al., 1999). Kitamura et al. (2004) used the largest  
10 sample and Sakamoto et al. (1998) found the same structure using confirmatory factor  
11 analytic techniques. The content captured by the factors reported in these studies, in  
12 particular those reporting a three-factor solution, relate to the content of diagnostic criteria  
13 of the DSM-5. For example, the cognitive symptom domain reflects the DSM-5 diagnostic  
14 criteria such as diminished ability to think or concentrate, or indecisiveness, and recurrent  
15 thoughts of death; the affective symptom domain reflects a depressed mood, feelings of  
16 worthlessness or excessive or inappropriate guilt and the somatic symptom domain reflects  
17 significant weight loss or gain, and insomnia or hypersomnia.

18       Therefore, in this study, we first sought to accumulate reproducible knowledge about  
19 the phenotypical structure of depression using exploratory and confirmatory factor analyses.  
20 Given these previous studies, we expected to find multiple factors rather than a single

1 factor. Additionally, we tested alternative factor solutions, including higher-order factor and  
2 bi-factor models, which both comprise general and specific factors and offer more  
3 parsimonious representations of the relationships between the multiple symptom domains  
4 of depression. Especially, a bi-factor analysis allows us (a) to simultaneously model  
5 depressive symptomatology at the general and the domain-specific levels, (b) to examine  
6 whether domain-specific factors retain any unique variance, unshared with other domains  
7 (e.g. Holzinger & Swineford, 1937).

8         Investigating genetic and environmental influences in depression is important  
9 because it can provide a modelling scheme that represents the complex and multi-factorial  
10 nature of symptom domain risks (Byers et al., 2009). A review of twin research prior to  
11 1999 from Australian, Swedish, British, and American samples by Sullivan et al. (2000)  
12 showed that depression has a heritable component that does not appreciably differ between  
13 community and clinical samples ( $h^2 = 37\%$  [95%CI: 28%, 42%] for community samples,  
14 and  $h^2 = 43\%$  [95%CI: 21%, 58%] for clinical samples). More recently, a study with a large  
15 sample of Scottish families demonstrated that the heritability of depression was between  
16 28% to 44% (Fernandez-Pujals et al., 2015), whereas in the US sample with an extended  
17 family design the heritability estimate of depressive symptoms was not significant ( $h^2 =$   
18 8.6% [95%CI: 0%, 57%, Byers et al., 2009). For non-Western countries, previous research  
19 found that the heritability of depression was also moderate, specifically ranging from 34%  
20 to 61%, except in the Sri Lankan male sample, where the heritability was only 4% (Ball et

1 al., 2009; Chen et al., 2014; Chen & Yu, 2015). However, interestingly, although factor  
2 analyses at the phenotypic level pointed toward the existence of multiple factors, almost all  
3 prior research on the aetiology of depression was based on the total score only, except for a  
4 few studies (e.g. McGue & Christensen, 1997). Therefore, few behavioural genetic studies  
5 on depression have taken into consideration the multi-dimensionality of depressive  
6 symptoms.

7 In this study, we aimed to examine the aetiological architecture of depressive  
8 symptoms based on findings from phenotypic confirmatory factor analyses. More  
9 specifically, the purpose of the present paper was three-fold. First, we examined the  
10 factorial structure of the SDS in a twin sample from a Japanese community sample to  
11 elucidate the phenotypic structure of depressive symptoms. We compared three  
12 hypothetical models (i.e. multiple-factor, higher-order factor, and bi-factor models; see Fig.  
13 1). Second, we estimated the relative influence of genetic and environmental influences on  
14 each domain of depression symptomatology assessed by the SDS. Third, we investigated  
15 the relationships between genetic and environmental influences underlying the depressive  
16 symptom domains to determine the role these factors play in their observed covariance.

## 17 **Method**

### 18 *Subjects and Questionnaires*

19 A mail survey was conducted as part of the ongoing longitudinal Keio Twin Study  
20 (KTS) for residents living mainly near the Tokyo area in Japan (see Ando et al., 2013). The

1 total number of participants was 425 twin pairs including 301 MZ twin pairs (211 female  
2 MZ, 87 male MZ, and 3 sex-unknown twin pairs) and 124 DZ twin pairs (56 female DZ, 26  
3 male DZ, and 42 opposite-sex twin pairs). The twins were 23.41 years old ( $SD = 4.24$ ). The  
4 participants completed the Japanese version of the SDS (20 items, 4-point Likert scale;  
5 Fukuda & Kobayashi, 1983; Zung, 1965) which is widely and commonly used to assess  
6 individual differences in depressive symptoms, adequately capturing multiple symptom  
7 domains (Cheung & Power, 2012). The descriptive statistics are shown in Table 1. As a  
8 whole, the scale was adequately internally consistent ( $\omega = .89$ ). The zygosity was  
9 determined by questionnaire items on the physical similarity and confusion of the twins by  
10 family members, friends and strangers (Ooki et al., 1990; Torgersen, 1979), and has been  
11 shown to categorise twin pairs correctly in over 93% of cases (Magnus et al., 1983; Ando et  
12 al., 2013).

### 13 *Twin Methods*

14 Heritability, or the proportion of the observed variability on a measure directly  
15 attributable to genetic influences is estimated by comparing within-pair similarity (such as  
16 with Pearson's  $r$ ) in MZ twins who share 100% of their genetic material to within-pair  
17 similarity in DZ twins who share on average 50% of their segregated genes (Knopik et al.,  
18 2016). Using structural equation modelling, the phenotypic variance can be decomposed  
19 into four components: additive genetic (A), non-additive genetic (D), shared environmental  
20 (C), and non-shared environmental (E) variance components. A estimates the additive



1 genetic effects on the phenotype of interest. D represents the interactive contribution of  
2 alleles within a single locus; C, or shared environment, estimates environmental influences  
3 that make twins similar, regardless of their zygosity; and E, or non-shared environment,  
4 represents environmental influences that make twins different, and also includes  
5 measurement error. To reveal which influences significantly contribute to phenotypic  
6 variances, five models were systematically compared. We fitted the ADE model, ACE  
7 model, AE model, CE model, and E model and evaluated the relative explanatory power of  
8 each model. Furthermore, to investigate the nature of the relationships between the multiple  
9 sets of symptom domains, we used multivariate genetic analyses to parameterise the  
10 variance and covariance between multiple symptoms at the same time. All the behavioural  
11 genetic analyses were performed on the raw data using the full information maximum  
12 likelihood estimation implemented in the R packages OpenMx 2.0 (Neale et al., 2016) and  
13 lavaan (Rosseel, 2012). The model fits were evaluated by using the chi-square index and  
14 Akaike's Information Criterion (AIC; Akaike, 1987) which is calculated by  $\chi^2 - 2df$  as well  
15 as the Bayesian Information Criterion (BIC, Schwarz, 1978; Sclove, 1987). The model with  
16 the lowest AIC and/or BIC indicates the best fit.

## 17 **Results**

### 18 *Descriptive Statistics and Exploratory and Confirmatory Factor Analyses*

19 The descriptive statistics for each SDS item are shown in Table 1. We first examined  
20 the age and sex differences in the total depressive symptoms score. We found no significant

1 correlation between age and the total SDS score ( $r = -.05, p = .18$ ), and no significant  
2 differences between the sexes ( $t(837) = 1.09, p = .28$ ). Although the effects of age and sex  
3 on depressive symptoms were statistically insignificant, the regression residuals obtained  
4 after controlling for these two factors were used in all of the following analyses (McGue &  
5 Bouchard, 1984).

6       The SDS items were subjected to maximum likelihood factor analysis with direct  
7 Oblimin rotation, using one twin randomly selected from each twin pair. Five items (i.e.  
8 [a]: I have trouble with constipation, [b]: Morning is when I feel the best [reversed item],  
9 [c]: I feel that others would be better off if I were dead, [d]: I find it easy to do the things I  
10 used to [reversed item], and [e]: I notice that I am losing weight) showed low factor  
11 loadings, which were less than .35 on all components and showed high complexity over 2.0,  
12 which means none of these five items could not contribute efficiently to a simple structure  
13 (Hofmann, 1978). A previous study also found that the first two items (i.e. [a] and [b]) had  
14 low loadings when a principal component analysis was conducted (Sakamoto et al., 1998).  
15 Item [c] should be classified in the affective symptom domain. However, in line with the  
16 previous study (Sakamoto et al., 1998), this was not loaded on any factors, maybe because  
17 the item exhibited a floor effect among the non-clinical samples (over two thirds of the  
18 sample answered “little or none of the time [1]” to this item) and the correlation between  
19 item [c] and other items became obscured. The content of item [d] is somewhat unspecific  
20 and hard to allocate to a specific symptom domain. Although item [e] can clearly be

1 included in the somatic symptom domain (American Psychiatric Association, 2013), in this  
2 sample, it was dropped as loading was  $< .35$  and complexity  $> 2.0$ . Therefore, these five  
3 items were removed from all subsequent analyses.

4 Our examination of a scree plot obtained with simulations implemented in the R  
5 package *psy* (Falissard, 2012) suggested three factors (Table 1 and Fig. 2). We next  
6 performed a confirmatory factor analysis using the R package *lavaan* (Rosseel, 2012). In all  
7 tested models, the factor loadings were equally constrained across twins and zygosity  
8 groups for each item of the depression scale, so that the same factor model was specified  
9 across twins in a pair and across zygosity groups (e.g. Olsen & Kenny, 2006; Wood et al.,  
10 2008). The three-factor model fitted reasonably well to the data, compared to other factor  
11 models. The first factor was defined by five items and could be interpreted as being within  
12 the cognitive symptom domain (e.g. “I find it easy to make decisions [reversed item]”). The  
13 second factor was defined by seven items and could be interpreted as the affective  
14 symptom domain (e.g. “I feel down-hearted and blue”). The third factor was defined by  
15 three items and could be interpreted as the somatic symptom domain (e.g. “I eat as much as  
16 I used to [reversed item]”). The resulting three-factor structure supports Zung’s (1965)  
17 original assumption, and replicated previous research (Kitamura et al., 2004; Sakamoto et  
18 al., 1998). McDonald’s  $\omega$  coefficients as measures of internal consistency were acceptable  
19 for all three symptom domains (.86 for cognitive, .86 for affective, and .59 for somatic).  
20 Additionally, the inter-factor correlations for the three-factor model were moderate, ranging

1 from .32 to .56.

2 We then compared a first-order three-factor model with higher-order three-factor and  
3 bi-factor models. The model fit indices for the confirmatory factor analyses are shown in  
4 Table 2. The results revealed that a bi-factor model explained the data more parsimoniously  
5 than the first-order three-factor and higher-order three-factor models. Table 1 also shows  
6 factor loadings for both the general and three specific factors. The standardised loadings on  
7 the general factor ranged from .19 to .76. This means that the general factor reflects a broad  
8 depressive symptomology. Items from the cognitive symptom domain loaded strongly on  
9 the general factor and only weakly on the specific factor, indicating that the general factor  
10 adequately captured the cognitive dimension. The affective items loaded similarly on the  
11 general and the specific factor. Items for the somatic symptom domain loaded more  
12 strongly on the specific factor as opposed to the cognitive symptom domain, indicating that  
13 the specific factor captured more of the variance in somatic items than the general factor.

#### 14 *Univariate Genetic Analysis*

15 The heritability of the total sum-score and the sum-scores reflecting the three  
16 dimensions are provided in Table 3. The results from the analyses including opposite sex  
17 DZ twins are presented as they were very similar to the results from the analyses excluding  
18 opposite sex twins. Estimates indicate that non-additive genetic and shared environmental  
19 effects were not detected for any symptom domain and that the AE model fitted the data  
20 best, which is consistent with prior empirical studies (e.g. Ball et al., 2009; Chen et al.,

1 2014, Kendler et al., 2013). The heritability of these symptoms ranged between .27 for the  
2 somatic symptom domain and .41 for the cognitive symptom domain.

### 3 *Multivariate Genetic Analysis*

4       Given that individual differences between the depressive symptom domains were  
5 explained by only additive genetic (A) and non-shared environmental (E) influences, the  
6 multivariate genetic analyses utilised in this section implemented an AE model.  
7 Additionally, on the basis of results from the phenotypic confirmatory factor analysis, we  
8 selected the best-fitting factorial structure for multivariate genetic modelling, namely a  
9 bi-factor solution including a general factor with three specific factors (i.e. cognitive,  
10 affective, and somatic symptom domains). As shown in Table 4, the variation in the general  
11 factor labelled depression was explained by the common genetic factor (47.0%), and by the  
12 non-shared environmental factor (53.0%). The symptom domain-specific genetic effect  
13 accounted for 29.4% of the variance only in the affective symptom domain, but no  
14 significant amount of variance in the cognitive and somatic symptom domains. The  
15 symptom domain-specific nonshared environmental effects, including the measurement  
16 error, were significant in all three symptom domains and explained the variance from  
17 69.6% to 81.8%. In sum, our results revealed a genetic contribution to the general factor of  
18 depression, suggesting a set of shared genetic effects across all items. Specific genetic  
19 influences were present only for the affective symptom domain. Moreover, in the general  
20 factor and even more so in the specific factors, non-shared environmental effects were

1 prominent.

## 2 **Discussion**

3 The aims of this study were: (a) to examine the factorial structure of the SDS in a  
4 Japanese twin sample; (b) to estimate the relative contributions of genetic and  
5 environmental influences on depressive symptoms dimensions; and (c) to investigate the  
6 multivariate genetic and environmental architecture underlying depressive symptom  
7 factors.

### 8 **Factorial structure of depression symptomatology.**

9 The results of our exploratory factor analysis yielded three factors describing  
10 cognitive, affective, and somatic symptomatology. This analysis demonstrated that in a  
11 Japanese sample, a three-factor solution describes depressive symptoms better. This is in  
12 line with Zung's (1965) original assumption and as reported by previous studies (Kitamura  
13 et al., 2004; Sakamoto et al., 1998). Moreover, findings from a series of confirmatory factor  
14 analyses supported the idea that a bi-factor model with a general factor and three specific  
15 factors fitted the data better than the other alternative models. This suggests that depression  
16 may be interpreted as a general psychological construct with three residual factors  
17 reflecting cognitive, affective, and somatic symptom domains. This general factor captured  
18 the variance in cognitive symptoms more fully, followed by affective symptoms and, to a  
19 lesser extent, somatic symptoms. Previous studies have reported that a bi-factor solution  
20 fits best to the data on other depression scales (e.g. Fong et al., 2016 for the Center for

1 Epidemiologic Studies Depression Scale, [CES-D], and McElory et al., 2018 for the Beck  
2 Depression Inventory II, [BDI-II]). Our study could contribute to the accumulating  
3 evidence that, across scales, depression appears more likely to have a bi-factor structure  
4 rather than a single factor, multiple factor, or higher-order factor structure.

5       Within a non-clinical setting, we were able to demonstrate that the structure of  
6 depressive symptomatology could be represented by a general factor, which captured  
7 individual differences across a broad range of depressive symptoms. In addition to this core  
8 general factor, three factors captured the specific variance shared by items within each of  
9 three dimensions— affective, cognitive, and somatic. If these findings can be replicated in a  
10 clinical sample, this implies that clinicians have to simultaneously attend to depression as a  
11 general construct while still attending to specific manifestations, which can be independent  
12 of the general construct and of each other. Namely, some patients may manifest somatic  
13 symptoms while not having elevated levels of affective and/or cognitive symptoms. As  
14 such, differential therapeutic strategies should ideally attend to differential symptomatic  
15 profiles.

16       **Genetic and environmental influences on cognitive, affective and somatic**  
17 **domains.**

18       Univariate genetic analyses for sum-scores reflecting each dimension were explained  
19 by additive genetic and non-shared environmental influences only. These results are  
20 congruent with those from a previous meta-analysis (Sullivan et al., 2000). Heritability

1 estimates were rather comparable, ranging from 29% to 41% for each of the three symptom  
2 domains, and approximately two thirds of the individual differences in each symptom  
3 dimension were explained by non-shared environmental influences (Ball et al., 2009,  
4 Fernandez-Pujas et al., 2015, Sullivan et al., 2000). Although several previous studies  
5 reported significant shared environmental influences (Chen et al., 2014; Happonen et al.,  
6 2002), they utilised children and adolescent twin pairs and their parents, whereas the  
7 present study was conducted in an adult sample.

#### 8 **Multivariate genetic architecture of depression symptomatology.**

9 *Genetic contributions.* We conducted multivariate genetic analyses based on the  
10 results of our exploratory and confirmatory factor analyses. In response to the best-fitting  
11 model suggested from our factor analyses at the phenotypic level, we fitted a bi-factor  
12 model to the data for behavioural genetic modelling. Previous twin research has shown that  
13 depression is substantially heritable. However, to the best of our knowledge, this is the first  
14 study fitting a bi-factor model within a twin design to examine the aetiology of depression.  
15 As shown in Table 1, almost all items loaded substantially on the general factor, suggesting  
16 that a common heritable factor may adequately reflect depression symptomatology. Our  
17 estimate of the heritability of the general factor of depressive symptoms was substantial  
18 (47.0% [95% CI: 36.8%, 57.1%]), with a higher point estimate than for any of the  
19 sum-score reflecting the symptom dimensions. Interestingly, the estimated heritability of  
20 the general factor from a bi-factor model was higher than that of the total sum-score. This



1 suggests that the use of bi-factor architecture reduced the measurement error for the general  
2 factor, enabling a better estimation of the aetiological components (Henry et al., 2016).  
3 Furthermore, our bi-factor model revealed that a significant specific genetic contribution  
4 was detected only for the affective symptom domain even though univariate genetic  
5 analyses had detected significant heritability for all symptom domains. This suggests that  
6 affective symptoms might be influenced by specific genetic influences not captured by the  
7 general factor, indicating a partial aetiological independence of the affective symptom  
8 domain from the general factor among a Japanese sample.

9 Overall and in line with the previous studies, our findings supported substantial  
10 heritability of the general factor for depressive symptomatology. A shared genetic risk for  
11 the general factor of depression may be linked to precursors of depressive symptomatology  
12 (e.g. neuroticism of personality traits, Luciano et al., 2018). By contrast, prior research on  
13 major depression assessed by personal interview (Kendler et al., 2013) revealed that major  
14 depression criteria from the DSM-IV did not reflect a single dimension of genetic liability,  
15 indicating that genetic influences on clinical criteria of major depression were  
16 heterogeneous and reflected the three underlying dimensions of major depression.  
17 Differences in results could reflect differences in methods, in particular assessment  
18 methods and fitted models because Kendler et al. (2013) did not fit a bi-factor model to  
19 their data.

20 Our findings of moderate genetic influences on the general factor, are consistent with

1 previous research demonstrating that depression is moderately heritable (Sullivan et al.,  
2 2000). We also found that specific factors were mostly influenced by non-shared  
3 environmental rather than genetic influences (except for the affective domain in our  
4 sample). Whether our findings of a bi-factorial structure and the corresponding estimates of  
5 genetic and environmental influences can be replicated using other depression scales  
6 remains to be fully investigated. So far, previous studies have shown that the CES-D and  
7 BDI-II have a bi-factor structure at the phenotypic level (Fong et al., 2016; McElory et al.,  
8 2018). Additional research is clearly needed in the area. If our findings are confirmed, two  
9 interpretations are plausible. First, the fact that the general factor is more heritable than the  
10 specific factors, which are mainly explained by the E component, may be due to  
11 measurement error. The E component includes both genuine non-shared environmental  
12 influences and measurement error. Consequently, the specific factors, which by definition  
13 rely on less items, may suffer more from measurement error, artificially lowering  
14 heritability and increasing non-shared environmental estimates. Alternatively, we can  
15 speculate that the general liability to depression is indeed more heritable, whereas specific  
16 manifestations of the disease (i.e. cognitive, affective or somatic) are more dependent on  
17 person-specific environmental influences. If verified, such a structure might contribute to  
18 explain cross-cultural differences in the clinical manifestations of the common liability to  
19 depression.

20 *Non-shared environmental contributions.* Non-shared environmental influences

1 accounted for half of the variance in the general factor, and 70 to 82% of the variance in the  
2 domain-specific factors. Importantly, estimates of non-shared environmental influences  
3 also include measurement error. These results raise the possibility that, while a general  
4 genetic factor largely accounts for the communality between symptoms of depression,  
5 non-shared environmental influences may explain most of the dimension-specific factors.  
6 According to prior available research, stressful life situations (e.g. individual loss  
7 experience such as a job or a beloved one, and interpersonal conflict at social contexts)  
8 could be plausible candidates of non-shared environmental triggers (Mazure, 1998 for a  
9 review). Therefore, the utility of such specific factors once the general factor is accounted  
10 for should be tested in further studies, for example, by testing whether specific factors  
11 uniquely associate with predictors and outcomes of depressive symptomatology.

### 12 **Strengths and limitations.**

13 The present study has several limitations. One limitation is that because of the  
14 relatively small size of the twin sample, we did not test for sex differences in the  
15 measurement and aetiological models. The development of depression may involve sex  
16 differences, and females generally do show a higher prevalence of depression. However,  
17 previous studies on the heritability of depression showed mixed results: several previous  
18 studies reported no differences in heritability between females and males (Agrawal et al.,  
19 2004; Chen & Yu, 2015; Foley et al., 2003), while other studies found that sex differences  
20 in heritability did exist (Kendler et al., 2001, 2006). Since a sex-limitation analysis in

1 behavioural genetic models can help answer the question of whether females and males are  
2 influenced by the same amount of genetic and environmental influences, further research  
3 with a larger sample size in Asian populations is needed. Another possible limitation is that  
4 the twin sample used in the present study is based on a healthy population sample, not a  
5 clinical sample. However, Kendler et al. (2006) and Sullivan et al. (2000) have suggested  
6 that findings from general population sample studies of depression are comparable to those  
7 of clinical sample studies, and research on depression symptomatology in non-clinical  
8 samples is important in its own right. Specifically, it can be argued that using a non-clinical  
9 sample allowed us to study the phenotypic and genetic architecture of individual  
10 differences in depression using a broad range of depression scores, whereas a clinical  
11 sample may entail range restrictions and reduced correlations.

## 12 **Conclusions.**

13 Despite the above limitations, by using a genetically informative sample, the present  
14 study extended previous findings in several ways. Confirmatory factor analyses at the  
15 phenotypic level confirmed the multidimensionality of individual differences in depressive  
16 symptoms and, in addition to a general factor, identified three residual factors reflecting  
17 three domains of depressive symptoms: cognitive, affective, and somatic. Most importantly,  
18 multivariate genetic modelling revealed that the general factor, which adequately reflected  
19 depressive symptomatology across dimensions, was moderately heritable, whereas domain  
20 specific factors were mostly influenced by non-shared environmental influences.

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8

### **Declaration of Interest**

9 None.

10

### **Ethical Standards**

11 The authors assert that all procedures contributing to this work comply with the ethical

12 standards of the relevant institutional committees on human experimentation and with the

13 Helsinki Declaration of 1975, as revised in 2008.

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- 9

1 Figure Captions

2 Fig. 1 Three tested models when conducting confirmatory factor analyses.

3 Fig. 2 Scree plotted eigenvalues with simulated random normal data (number of iterations

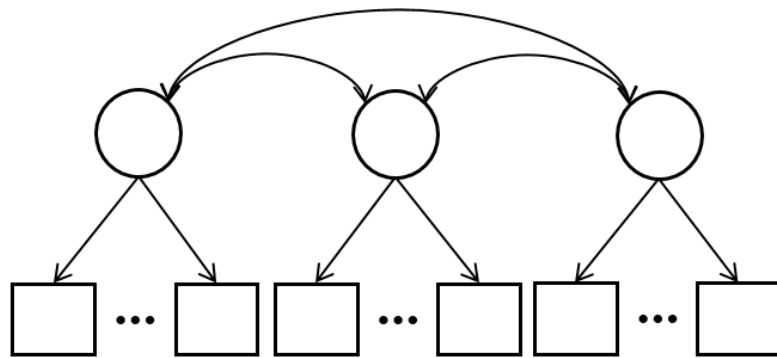
4 = 20)

5

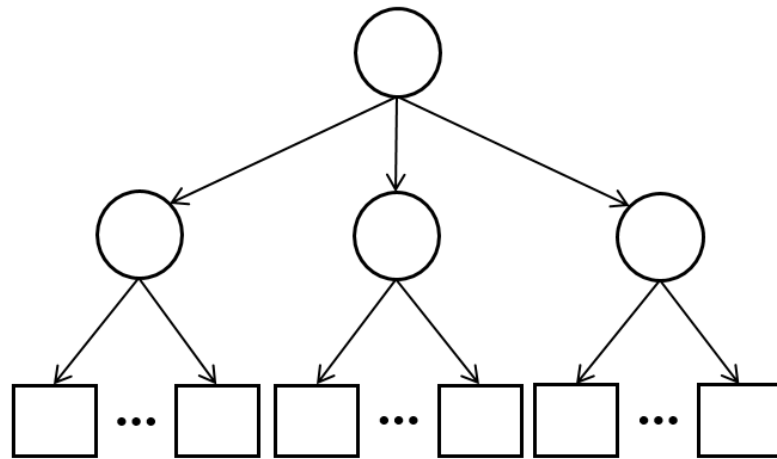
1 Fig. 1.

2

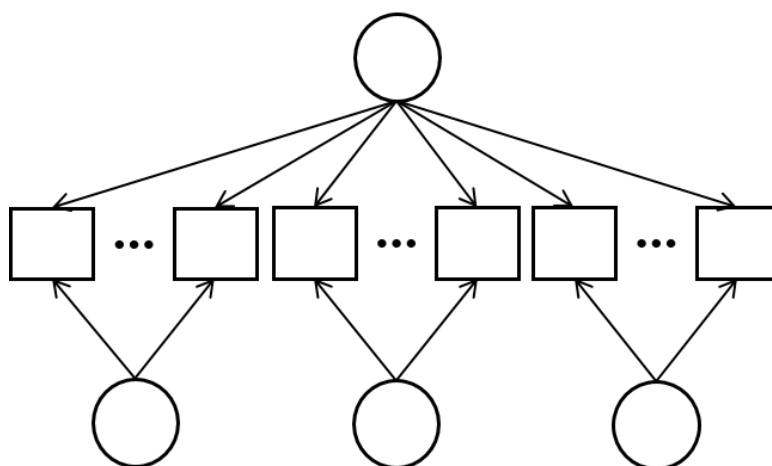
3



a) simple correlated three factor solution

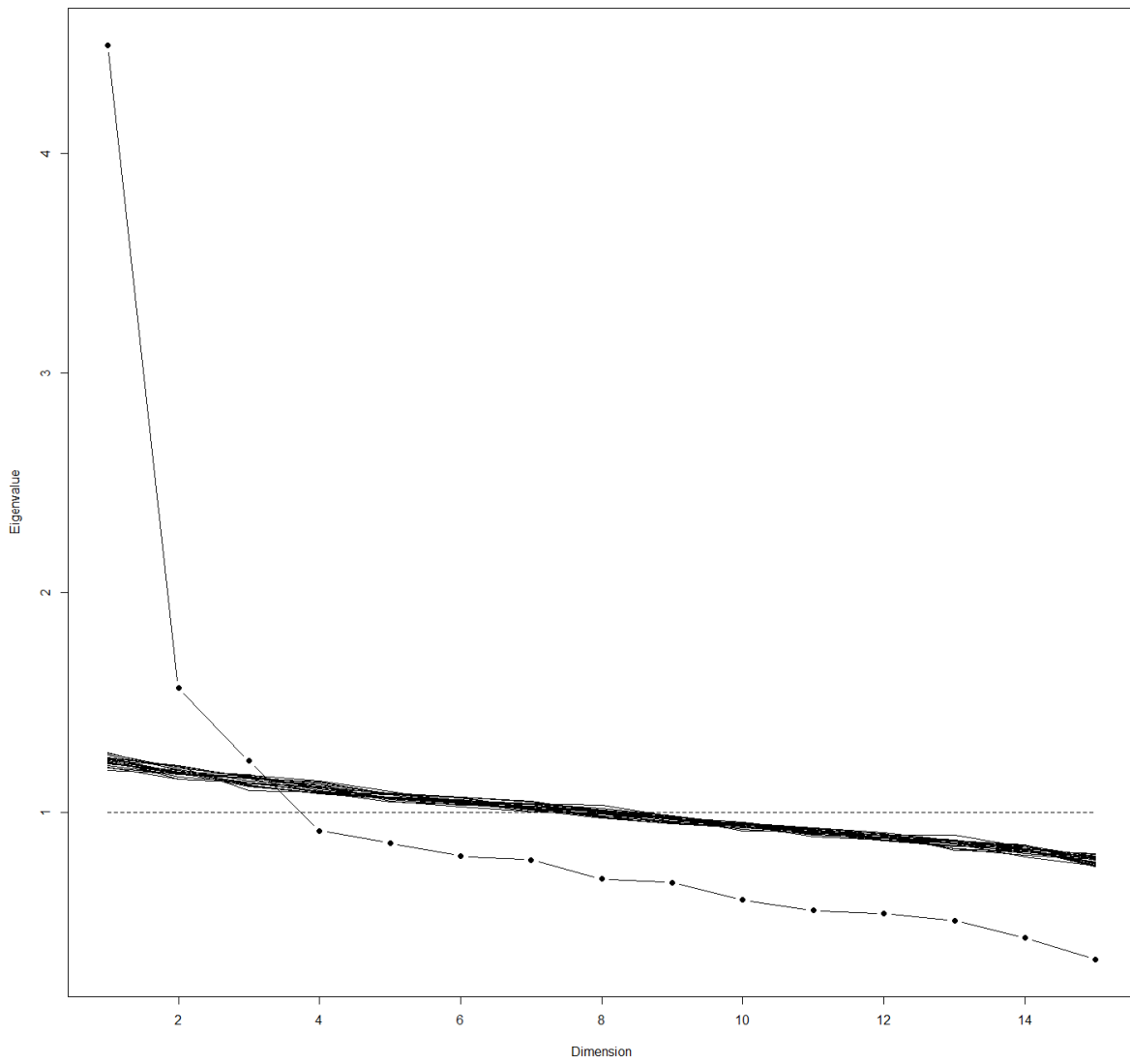


b) higher-order factor solution



c) bi-factor solution (or general-specific)

1 Fig. 2.



2

1 Table 1 Exploratory and confirmatory factor analyses for depressive symptoms with  
 2 descriptive statistics

	<i>Mean</i>	<i>S.D.</i>	EFA			CFA with a bi-factor solution			
			F1	F2	F3	G	C	A	S
F1: cognitive symptom domain ( $\omega = .86$ )									
I still enjoy the things I used to do (R)	2.35	.90	.74	.01	.03	.76	.62		
My life is pretty full (R)	2.26	.91	.74	.05	.03	.74	.16		
I feel hopeful about the future (R)	2.23	1.01	.62	-.04	.02	.65	-.10		
I feel that I am useful and needed (R)	2.32	.92	.60	-.01	-.04	.62	-.13		
I find it easy to make decisions (R)	2.69	.89	.41	.07	-.07	.49	-.15		
F2: affective symptom domain ( $\omega = .86$ )									
I have crying spells or feel like it	2.02	1.00	-.10	.67	.00	.30		.55	
I am more irritable than usual	1.91	.93	.01	.65	.03	.40		.55	
I feel down-hearted and blue	2.16	.98	.18	.65	-.01	.54		.51	
I get tired for no reason	2.79	.97	.00	.49	.04	.32		.40	
My mind is as clear as it used to be (R)	2.53	.90	.28	.46	-.05	.53		.34	
My heart beats faster than usual	1.57	.82	-.07	.45	.14	.25		.40	
I am restless and can't keep still	1.90	.93	-.07	.44	.12	.24		.39	
F3: somatic symptom domain ( $\omega = .59$ )									
I eat as much as I used to (R)	1.39	.69	.03	.04	.49	.23			.53
I have trouble sleeping at night	1.93	1.06	.03	.13	.47	.28			.39
I still enjoy sex (R)	1.94	.90	.17	-.19	.35	.19			.30
Removed									
Morning is when I feel the best (R)	3.06	.87							
I notice that I am losing weight	1.76	.93							
I have trouble with constipation	1.93	1.09							
I find it easy to do the things I used to (R)	1.93	.86							
I feel that others would be better off if I were dead	1.46	.76							
			F1	—					
inter-factor correlations			F2	.56	—				
			F3	.37	.32	—			

3  
 4 *Note.* R: reversed items.  $\omega$ : McDonald's omega coefficients. EFA: Exploratory Factor  
 5 Analysis. CFA: Confirmatory Factor Analysis. Standardized factor loadings are presented  
 6 for EFA and CFA. The CFA model presented here is a bi-factor solution, with G, C, A, S  
 7 standing for the general, cognitive, affective, and somatic factors respectively. Values in the  
 8 bottom three rows indicate inter-factor correlations when applying exploratory factor  
 9 analysis.

10

11



1 Table 2 Model fit indices to compare four confirmatory factor analyses

	AIC	sample-size adjusted BIC	RMSEA	SRMR
a) three-factor solution	30673.744	30741.367	.035	.049
b) higher-order factor solution	30674.509	30733.462	.035	.052
<b>c) bi-factor solution</b>	<b>30631.840</b>	<b>30714.200</b>	<b>.033</b>	<b>.045</b>

2

3 *Note:* AIC: Akaike's Information Criteria, BIC: Bayesian Information Criteria, RMSEA:

4 Root Mean Square Error of Approximation, SRMR: Standardized Root Mean Square

5 Residual. Bold face indicates the best fitting model.

1 Table 3 Genetic and environmental influences on sum-scores indicating three symptom  
 2 domains and a total score for depression

	Models	$a^2$	$d^2$	$c^2$	$e^2$	-2LL	df	AIC	BIC
cognitive symptom domain	ADE	.30 (.00 - .49)	.11 (.00 - .50)	—	.59 (.50 - .69)	4475.427	843	2789.427	-626.485
	ACE	.41 (.12 - .49)	—	.00 (.00 - .00)	.59 (.51 - .69)	4475.558	843	2789.558	-626.353
	<b>AE</b>	<b>.41</b> <b>(.31 - .49)</b>	—	—	<b>.59</b> <b>(.51 - .69)</b>	<b>4475.558</b>	<b>844</b>	<b>2787.558</b>	<b>-632.405</b>
	CE	—	—	.32 (.23 - .40)	.68 (.60 - .77)	4482.712	844	2794.712	-625.251
	E	—	—	—	1	4528.903	845	2838.903	-585.112
affective symptom domain	ADE	.20 (.00 - .40)	.11 (.00 - .41)	—	.69 (.59 - .79)	4821.951	843	3135.951	-279.961
	ACE	.31 (.00 - .41)	—	.00 (.00 - .28)	.69 (.59 - .79)	4822.055	843	3136.055	-279.856
	<b>AE</b>	<b>.31</b> <b>(.21 - .41)</b>	—	—	<b>.69</b> <b>(.59 - .79)</b>	<b>4822.055</b>	<b>844</b>	<b>3134.055</b>	<b>-285.908</b>
	CE	—	—	.26 (.16 - .34)	.74 (.66 - .84)	4825.644	844	3137.644	-282.320
	E	—	—	—	1	4854.198	845	3164.198	-259.817
somatic symptom domain	ADE	.18 (.00 - .38)	.12 (.00 - .39)	—	.70 (.61 - .81)	3401.399	842	1717.399	-1694.460
	ACE	.29 (.00 - .39)	—	.00 (.00 - .29)	.71 (.61 - .81)	3401.495	842	1717.495	-1694.365
	<b>AE</b>	<b>.29</b> <b>(.19 - .39)</b>	—	—	<b>.71</b> <b>(.61 - .81)</b>	<b>3401.495</b>	<b>843</b>	<b>1715.495</b>	<b>-1700.417</b>
	CE	—	—	.25 (.16 - .34)	.75 (.66 - .84)	3404.381	843	1718.381	-1697.530
	E	—	—	—	1	3431.302	844	1743.302	-1676.661
total depression score	ADE	.21 (.00 - .48)	.19 (.00 - .49)	—	.60 (.51 - .71)	5763.317	840	4083.317	679.562
	ACE	.39 (.12 - .48)	—	.00 (.00 - .00)	.61 (.52 - .71)	5763.657	840	4083.657	679.902
	<b>AE</b>	<b>.39</b> <b>(.29 - .48)</b>	—	—	<b>.61</b> <b>(.52 - .71)</b>	<b>5763.657</b>	<b>841</b>	<b>4081.657</b>	<b>673.850</b>
	CE	—	—	.31 (.22 - .39)	.69 (.61 - .78)	5770.963	841	4088.963	681.156
	E	—	—	—	1	5812.797	842	4128.797	716.938

3

4 *Note.* Numbers in parentheses show 95% confidence intervals.  $a^2$  = additive genetic effect,

5  $d^2$  = non-additive genetic effect,  $c^2$  = shared environmental effect,  $e^2$  = non-shared

6 environmental effect.  $-2LL = -2 \times \text{Log Likelihood}$ ,  $-2LL$  follows a  $\chi^2_{df}$  distribution,  $df =$

- 1 degree of freedom, AIC = Akaike's information criteria, BIC = Bayesian information
- 2 criteria. Bold faces indicate best fitting models.

1 Table 4 Genetic and non-shared environmental parameters on each factor from the bi-factor  
 2 solution.

3

	$a^2$	$e^2$
General factor of depression	.470 [ .368, .571 ]	.530 [ .429, .632 ]
Cognitive-specific symptom domain	.182 [ .000, .515 ]	.818 [ .485, 1.000 ]
Affective-specific symptom domain	.294 [ .145, .471 ]	.706 [ .529, .855 ]
Somatic-specific symptom domain	.304 [ .000, .649 ]	.696 [ .351, 1.000 ]

4

5