Review Article (invited as an award recipient in 2022)

Behaviour genetic studies of *kaigo yobo*: Focus on the difference between *tojikomori* and depression

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Abstract

As Japan is one of the most rapidly ageing countries in the world, there is an increasing need for long-term care. Accordingly, all municipalities in Japan have been required to start *kaigo yobo* programmes, which aim to prevent disability and increase healthy life expectancy among the aged. A typical *kaigo yobo* programme provides interventions for various conditions, including *tojikomori* (a Japanese term for the state of being housebound) and depression. However, no studies have found that *tojikomori* and depression interventions have the same effect, and the genetic factors for *tojikomori* remain unclear. Therefore, using the classical twin method, this study aims to investigate the genetic and environmental correlations between *tojikomori* and depressive symptoms and to clarify the mechanisms underlying the onset of *tojikomori*. Two analyses were performed: the first using structural equation modelling and the second investigating the associations between *tojikomori* and depressive symptoms in regard to genetic and environmental factors. The findings revealed that only two genetic factors explained all phenotypes loaded, which suggested that decomposing the relationships between the phenotypes correlated with depression into genetic and environmental factors of many other phenotypes makes it possible to determine the high-risk genetic backgrounds represented by combinations of other phenotypes. These results suggest that describing the genetic and environmental correlations between target (e.g. *tojikomori*, depression) and surrounding phenotypes could lead to the development of more effective individualised *kaigo yobo* programmes.

Keywords:
kaigo yobo, twin study, tojikomori, depression

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Introduction

Life expectancy has been steadily increasing in Japan. As of 2019, life expectancy was 81.41 years for males and 87.45 years for females. However, various age-related health problems are also becoming a social problem in regard to healthy life expectancy. In 2019, according to the Ministry of Health, Labour and Welfare (MHLW) in Japan, healthy life expectancy was 72.68 years for males and 75.38 years for females. Additionally, the ageing rate in Japan is rapidly increasing compared with other developed countries. The ageing rate was 7% in 1970, 14% in 1994, 21% in 2007 and 28.9% in 2022. By comparison, the ageing rate was 7% in France in 1889, and 126 years later, in 1990, had only reached 14%. Rapid ageing is accompanied by the increasing need for "long-term care" and expected increases in medical and long-term care costs for the aged (Ministry of Health, 2022). Since 2000, long-term care services have been separate from medical services and covered by long-term care insurance. However, in 2025, "baby boomers" will reach the mean age of 75 years, making this situation more critical. In addition to the rapid increase in the numbers of individuals requiring long-term care, it is predicted that there will be a shortage of social resources because of decreases in the working population and insurance income.

The Japanese Long-Term Care Insurance Act has two primary objectives: to provide insurance and to provide preventive care. Article 2 of the Act states that "(1) Long-Term Care Insurance shall provide necessary insurance benefits for a Condition of Need for Long-Term Care or for a Needed Support Condition of the insured person. (2) Insurance benefits as set forth in the preceding paragraph shall be provided in order to contribute to reduction or prevention of aggravation of a Condition of Need for Long-Term Care or a Needed Support Condition, and shall be provided with careful attention to cooperation with medical care."

Since 2006, all municipalities in Japan have been required to start what are referred to as *kaigo yobo* programmes, which aim to help prevent disability and increase healthy life expectancy among the aged, thereby alleviating the need for long-term care insurance. For *kaigo yobo*, the MHLW recommends focusing on the following six different functions: physical function, nutrition, oral function, *tojikomori* (a Japanese term for the state of being housebound), depression and dementia. A typical *kaigo yobo* intervention is to provide a group session that includes all six functions. However, no evidence has been published to suggest that *tojikomori* and depression interventions have the same effect. For example, a common intervention for an acute treatment period for depression is rest. By contrast, a common intervention for *tojikomori* in the aged is to promote going out and increasing contact with others; these intervention methods contradict each other.

The development of disease in humans has a complex association with genetic and environmental backgrounds. However, the genetic factors for *tojikomori* remain unclear. Understanding individual differences between *tojikomori* and depression is therefore essential for the implementation of interventions or preventive care by health professionals. The conventional epidemiological research methods used for comparing completely different genetic backgrounds have yet to clarify the influence of genetic and environmental factors. However, behavioural genetics, especially the twin study method, enables the relative importance of genetic and environmental factors to be estimated for each symptom.

What is *tojikomori*?

The exact meaning of *tojikomori* differs slightly from that of "housebound", which is generally caused by impaired physical and/or mental functions; no such limitations exist or are observed in relation to *tojikomori*. Therefore, "social isolation" is a more accurate description of *tojikomori* because this term encompasses not only the state of being housebound physically, but also the state of having less communication with others. However, the terms *tojikomori* and "housebound" are frequently used interchangeably. In this article, the term *tojikomori* is based on the following factors provided by (Kondo & Hirai, 2007): (1) the extent of daily activity, (2) the frequency of going out, (3) the frequency of contact with others and (4) mobility. The term describes older adults in Japan who are housebound but

have no impairments in physical function or major mental problems. Thus, the definition of *tojikomori* in this article is as follows: (1) A decreased frequency of going out (less than once per week), (2) a decreased frequency of contact with others (less than once per week) and (3) no impairments in physical function or major mental problems.

Previous studies (Hirai, Kondo, & Hanibuchi, 2008; Watanabe et al., 2005) have reported the prevalence of *tojikomori* in Japan to be between 8% and 21%. Longitudinal studies have reported that prolonged *tojikomori* leads to physical dysfunction and mental problems such as decreased activities of daily living (ADL) and instrumental ADL, cognitive function and depression (Herr, Latouche, & Ankri, 2013; Imuta et al., 1998; Shinkai et al., 2005; Watanabe et al., 2005).

Several causes of *tojikomori* have been identified, including physical factors (e.g. decreased walking ability, instrumental ADL, cognitive function), psychological factors (e.g. decreased subjective health, tendency for depression, lack of *ikigai* [purpose in life]) and social factors (e.g. old age, not participating in group activities, lower social and domestic roles) (Yasumura, 2009).

These previous Japanese studies have indicated that *tojikomori* leads to a negative spiral of frailty that can be prevented. However, to our knowledge, there are no such reports from other countries; instead, loneliness and social isolation have recently become issues in the same context. Whether *tojikomori* is the same as loneliness and social isolation still needs to be clarified. This is one reason for using the term *tojikomori* instead of housebound, loneliness or social isolation in the present article. What is clear, however, is that staying at home weakens physical and mental function, and individuals who choose to stay at home or communicate less frequently with others might have a reason to avoid something more serious, such as the onset of conditions such as depression. Therefore, to clarify the relationship between *tojikomori* and depression, the correlation with the genetic and environmental factors needs to be examined to clarify the mechanisms underlying the onset of *tojikomori*. Furthermore, expanding this clarification to other phenotypes might promote the development of more effective *kaigo yobo* programmes.

A longitudinal twin study on *tojikomori* and depressive symptoms in Japanese older adults (Inui et al., 2016)

This study was conducted to investigate the genetic and environmental correlations between *tojikomori* and depressive symptoms. Two analyses were performed using the classical twin method.

The first analysis performed was structural equation modelling (SEM) (Rijsdijk & Sham, 2002) to evaluate the relative importance of genetic and environmental factors for the phenotypes measured, that is, a cross-sectional evaluation of univariate measures. In SEM analyses, phenotypic variance is assumed to be divisible into four components: 1) an additive genetic component (A), 2) a non-additive genetic component (D), 3) a shared environmental component (C) and 4) a non-shared environmental component (E). Component A reflects the sum of the additive allelic effects of many segregating genes, whereas component D refers to the interaction of alleles. Component C, common to both types of twins, is shared by siblings in a family and expected to contribute equally to the similarities in monozygotic and dizygotic twin pairs. Component E, unique to each twin, is specific to each individual and expected to contribute to differences within pairs. Component E also includes measurement errors. Because components C and D cannot be estimated in the same model with twins reared together, ACE and ADE models were fitted as alternatives. The aim of genetic modelling is to identify a model that fits the data well and has as few explanatory parameters as possible. In the present study, we selected the ACE model for further discussion because it provides a better fit to the data than the ADE model. The ACE model considers the following possible combinations of parameters: ACE, AE, CE and E (Jang, 2005). The full model (i.e. the ACE model), which includes all latent variables, was tested against nested sub-models (i.e. AE, CE and E) with a reduced number of parameters. The fits of the alternative models were compared with the difference in −2 log likelihood (−2LL), which is asymptomatically distributed as χ^2 with degrees of freedom equal to the difference in the number of parameters. The fits of the different models were also tested by analysing Akaike's

information criterion (Akaike, 1987), in which a smaller value indicates a better model. The theoretically most acceptable and parsimonious model obtained estimates with 95% confidence intervals (CIs).

The results from the first analysis indicated that the AE model was the best-fitting model for all phenotypes. Regarding *tojikomori*, 29% of the variance was explained by additive genetic effects and 71% by unique environment (including error) effects at baseline in 2008. A 2012 follow-up showed similar results: 25% of the variance was explained by additive genetic effects and 75% by unique environment (including error) effects. Regarding depressive symptoms, 27% of the variance was explained by additive genetic effects at baseline and 28% at follow-up. Those results demonstrated that *tojikomori* is affected by additive genetic factors, which marks the first time the heritability of *tojikomori* has been estimated. To clarify the mechanisms underlying the onset of *tojikomori*, the other phenotypes genetically and environmentally related to *tojikomori* need to be clarified. Especially at this point, the greatest concern is whether depression and *tojikomori* share the same genetic background.

The second analysis investigated the associations between *tojikomori* and depressive symptoms in regard to genetic and environmental factors. A Cholesky decomposition (also known as a triangular decomposition) is useful for decomposing the relations between phenotypes genetically or environmentally. In a Cholesky decomposition, the first latent factor (i.e. A1, C1 or E1) loads on all the variables, the second on all but the first variable (i.e. excludes phenotype 1), and so on. In this study, three phenotypes were loaded to investigate the longitudinal influence of *tojikomori* on depression (i.e. *tojikomori* at baseline as phenotype 1, *tojikomori* at follow-up as phenotype 2 and depressive symptoms as phenotype 3). Furthermore, to investigate the effect of depression on *tojikomori*, the variables were exchanged (i.e. depressive symptoms at baseline as phenotype 1, depressive symptoms at follow-up as phenotype 2 and *tojikomori* at follow-up as phenotype 3).

The main results from the second analysis are shown in Figures 1 (effect of depression on *tojikomori*) and 2 (effect of *tojikomori* on depression). As shown in Figure 1, *tojikomori* was influenced by some common genetic factors with depressive symptoms (i.e. A1: 11% of the total variance), but not by others (i.e. A3: 30% of the total variance). Latent factor A2 was removed because its value could not be estimated, which indicates no additive genetic influence of depressive symptoms over time. This finding suggests that for the prevention of and interventions for *tojikomori*, persons in a genetic high-risk group for depressive symptoms need to be identified. As shown in Figure 2, *tojikomori* was influenced by genetic factors that increased with time, which was an interesting finding. In contrast to depressive symptoms, genetic influences do not typically change over time. Supposing that *tojikomori* is explained by a single genetic factor (not a single gene, but a single factor that includes multiple genes), in this

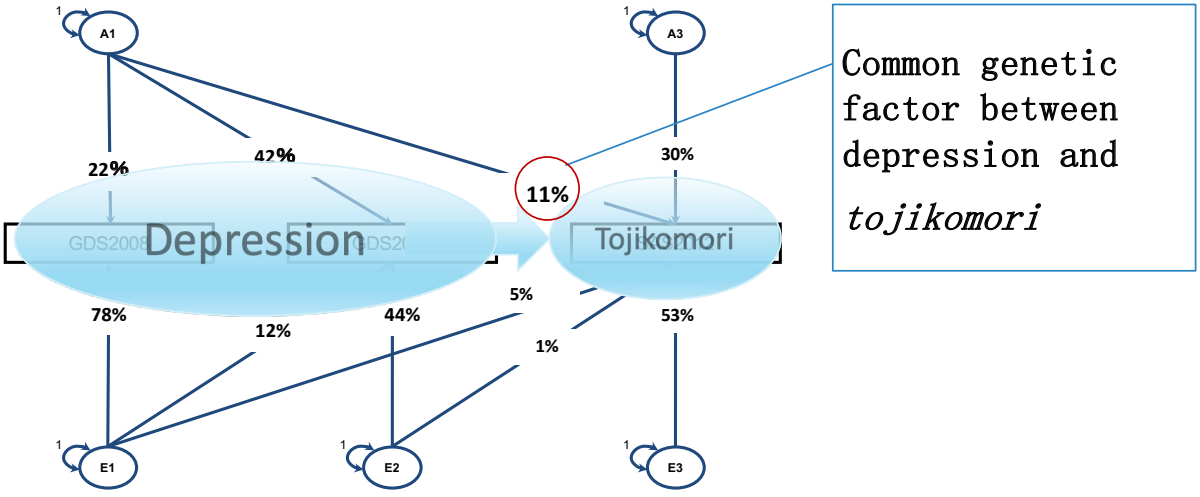

Fig. 1. Longitudinal effect of depression on future *tojikomori*. Modified from (Inui et al., 2016).

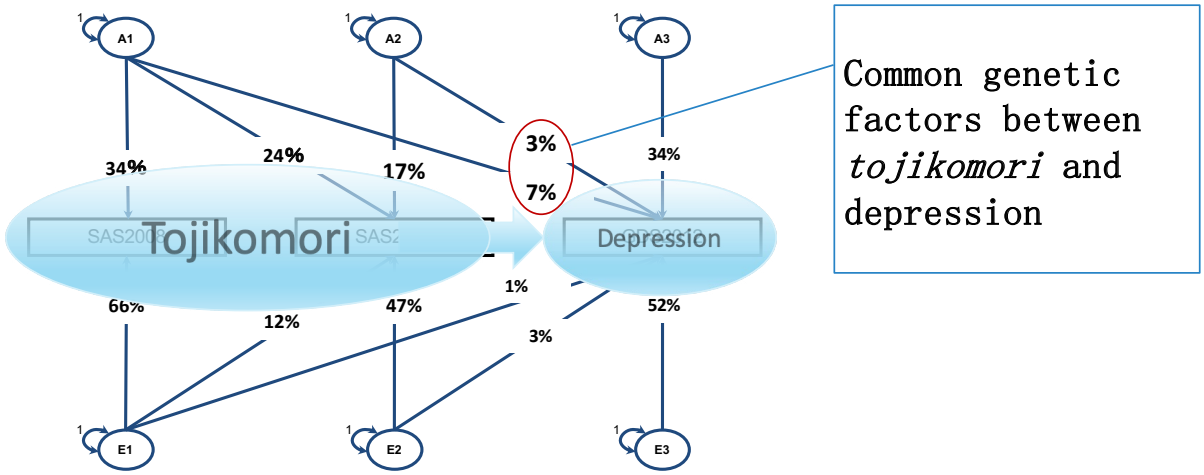

Fig. 2. Longitudinal effect of *tojikomori* on future depression. Modified from (Fujio Inui, 2016; Inui et al., 2016).

model, only A1 explained the genetic factor at follow-up, and thus, a22 from A2 might be more minor or even insignificant. However, A2 existed with 17% of 41% of the additive genetic effect of the *tojikomori* phenotype at follow-up. This result has no evident interpretation but could have significant implications in the future as research on *tojikomori* progresses.

Figure 3 shows standard interventions (e.g. group sessions) that aim to promote going outside and communicating more frequently with others to reduce *tojikomori* symptoms. However, some interventions may worsen situations for those with a high-risk genetic background for depression. Figure 4 shows future possibilities regarding individualised *kaigo yobo* programmes given the possibility of identifying high-risk genetic backgrounds for depression in terms of *tojikomori*. The intervention shown considers the genetic risk of depression. However, at present, no method exists to examine the genetic risk of depression in terms of *tojikomori*, so it is still important to clarify the phenotypic correlations in relation to genetic and environmental effects to elucidate the mechanisms underlying the onset and worsening of symptoms.

What is the genetic background of depression?

A previous meta-analysis of twin research studies reported that the heritability rate for depression was 37% (95% CI: 31%–42%) (Sullivan, Neale, & Kendler, 2000); however, heritability was still missing. Another study reported that “GWASs using large sets of samples, including thousands of patients with different forms of depressive disorders (DDs) and tens of thousands of patients

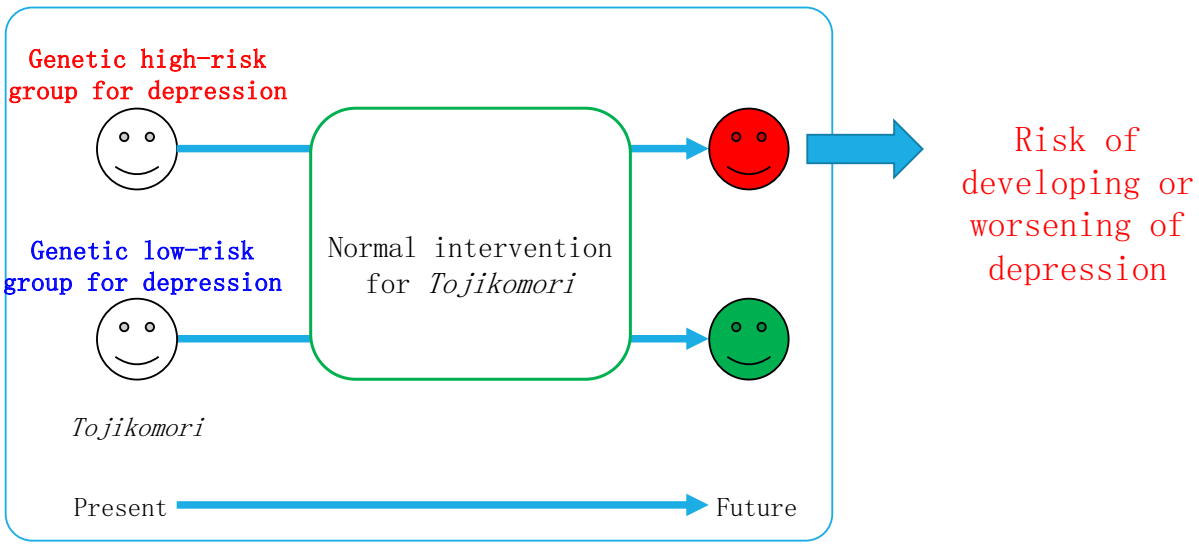

Fig. 3. Normal intervention for *tojikomori*.

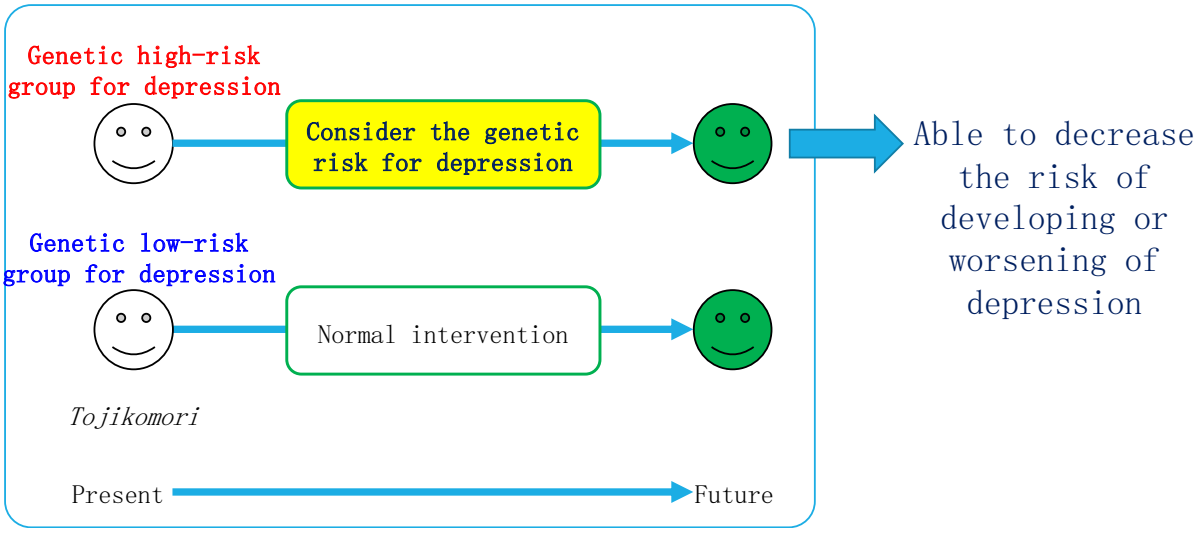

Fig. 4. An individualised intervention for *tojikomori*.

in meta-analyses, have failed to identify any specific loci responsible for predisposition to DDs" (Shadrina, Bondarenko, & Slominsky, 2018). Omics research may solve this mystery in the near future. However, it is also essential to consider other methodologies. The classical twin method still provides important answers. Several studies using the classical twin method have confirmed some "strange" results. For example, one study reported the genetic structure of four temperaments and depression; when the phenotypic correlations decomposed to genetic and environmental factors, the genetic factors that explained depression disappeared (Ono et al., 2002). In this study(Fujio Inui, 2016) showed similar results. Figure 5 shows the relationship between self-efficacy, fatigue and depressive symptoms decomposed to genetic and environmental factors. As shown in the figure, the genetic factors that explain depression have disappeared. In the present study, only two genetic

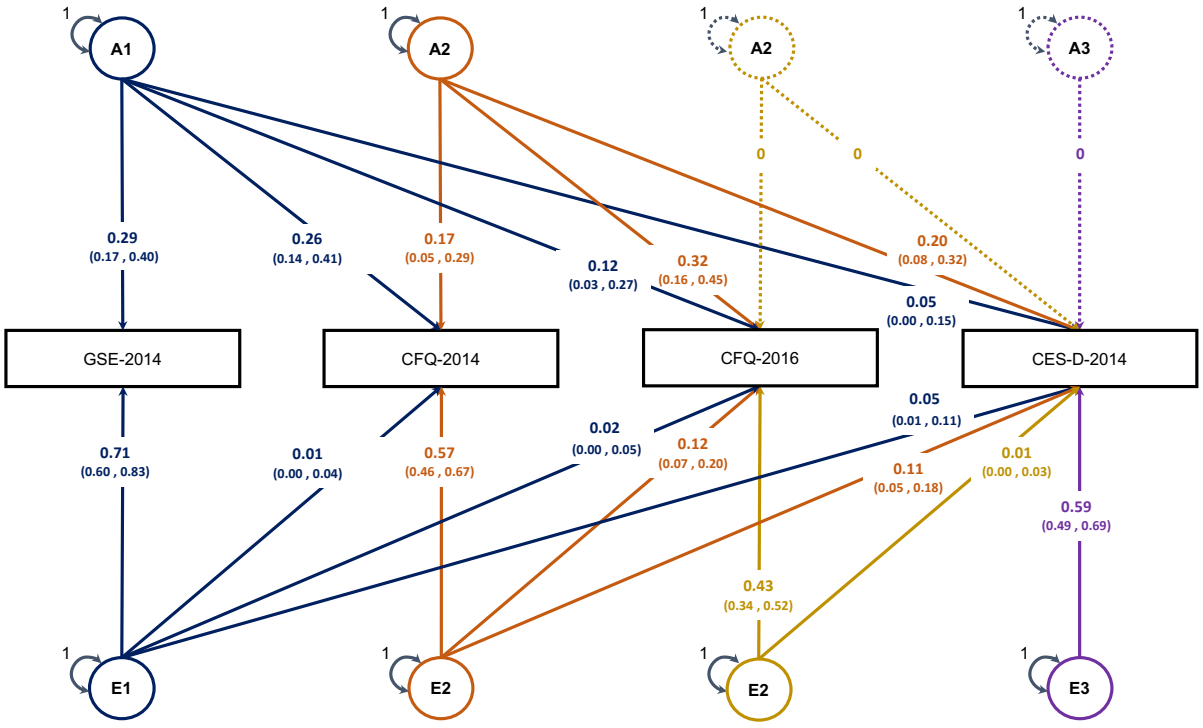

Fig. 5. Relationship between self-efficacy, fatigue and depressive symptoms decomposed to genetic and environmental factors. Modified from (Fujio Inui, 2016).

factors explained all phenotypes loaded. From these results, even without hunting for depression genes, decomposing the relationships between the phenotypes correlated with depression into genetic and environmental factors of many other phenotypes, it is possible to determine the high-risk genetic backgrounds represented by combinations of other phenotypes.

Aiming for individualised *kaigo yobo* programmes

Describing the genetic and environmental correlations between target phenotypes (e.g. *tojikomori*, depression) and other surrounding phenotypes could lead to the development of individualised *kaigo yobo* programmes. For example, previous studies have found that depressive symptoms are genetically correlated with social activities (Nishihara et al., 2011), *tojikomori* (Inui et al., 2016), general self-efficacy and fatigue (Fujio Inui, 2016).

Although these genetic relations remain insufficient to describe the high-risk backgrounds for depression, theoretically, this may be possible if appropriate results can be accumulated. This could make it possible to obtain epidemiological answers (i.e. individual genetic or environmental risk factors for the target phenotype) without the need to wait for molecular genetic studies, such as gene hunting, polygenic risk score or omics studies. Until recently, this method was the mainstream in behavioural genetics research. However, recently, there has been a shift towards omics research, which aims to explain mechanisms directly. However, the classical twin research method is still a valuable tool for the health science field.

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