● 多因子遺伝病研究の手法

(3) 双生児研究法

石川県立看護大学 健康科学講座 助教授
大木 秀一 Syuichi Ooki

要 旨

双生児研究法は多因子性疾患の遺伝的背景の解明に大きな役割を果たしてきた．最大の利点は遺伝要因と環境要因および両者の交互作用をマクロからミクロレベルまで把握しうる点である．① 統計遺伝学的解析手法の大幅な進歩，② 分子遺伝学的な解析手法との連動，③ ツインレジストリーをもとにした population-based な研究の推進，により近年その新たな可能性がクローズアップされている．

はじめに

双生児研究法は人類遺伝学の分野でも歴史の古い研究方法であり，ヒトのさまざまな形質に対する，遺伝要因と環境要因の寄与を推定する方法として多くの知見を与えてきた[1~3]．特にポストヒトゲノム計画の段階に入り，ゲノム情報の応用が単一遺伝子性疾患から多因子性疾患の発症機序の解明にシフトされつつある現在[4]，双生児研究法の新たな役割がクローズアップされている．

キーワード：双生児研究法，統計遺伝学，分子遺伝学，遺伝疫学，ツインレジストリー

双生児の種類と卵性診断

ヒトの双生児には，一卵性双生児（MZ）と二卵性双生児（DZ）の2種類がある．MZ は，もともと1個体として発育すべき1つの受精卵が卵割の初期に，多胚化を起して2個体として発育したものである．一方，DZ は2個の受精卵が同一の子宮内で発育したものである．双生児の二人が共有するゲノムの割合は MZ ペアでは 100％ であり，DZ ペアでは通常の兄弟姉妹と同じく平均して 50％ である．ヒトにおいてゲノムが完全に等しい個体は一卵性の多胎以外にはありえない．

双生児研究法の基本原理

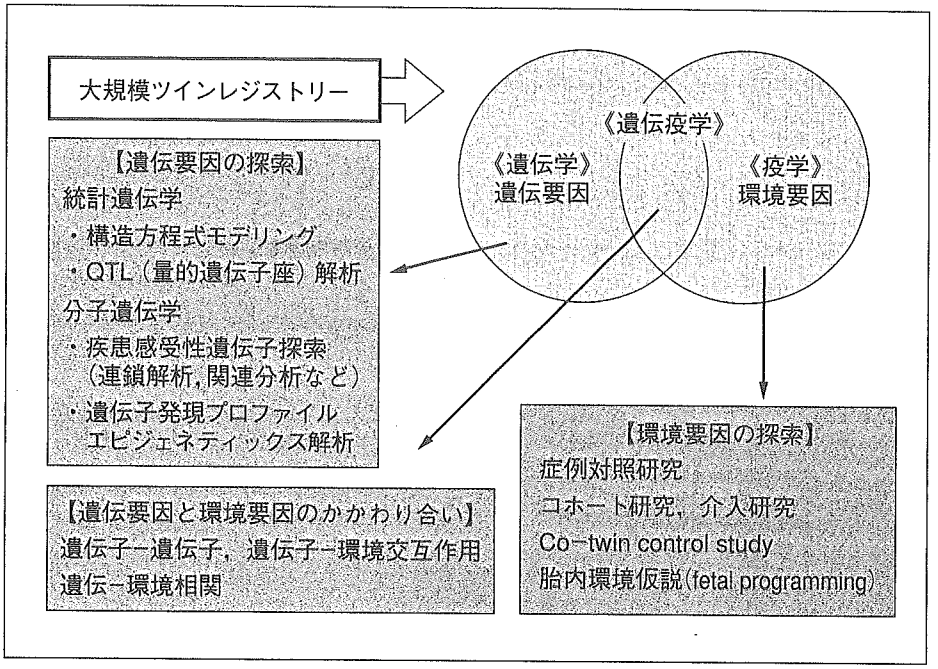
① MZ ペアにおいて疾患の不完全一致が見られるとき，それらをもたらした特異的な環境要因を分析できる．

② 双生児ペアについて二人の表現型の類似する程度を比較する．MZ ペア内の差は環境要因によるが，DZ ペア内の差は遺伝要因と環境要因の両者による．MZ ペアと DZ ペアの類似度（級内相関係数や発端者一致率）を比較することで，遺伝要因（A：相加的遺伝要因，D：非相加的遺伝要因）と環境要因（C：共有環境要因，E：非共有環境要因）の相対的な関与の程度を推定することができる[2]．異性 DZ ペアを解析に含めば性に特異的な遺伝要因の存在が検討できる．双生児研究法を用いれば，高次で複雑な心理・行動上の形質あるいは生活習慣病などに対するゲノム全体の影響を，自然の与えた実験的状況として分析可能である．

統計遺伝学的に多因子性疾患を解析する場合には，量的遺伝学のポリジーンモデルと易罹病性をもとにした閾値形質モデルが基本となる．近親ペアの遺伝的な距離と類似度の関係から，分散として表現される遺伝要因の割合を統計的に推定できる（遺伝率研究）．

多因子性疾患の病因論においては「遺伝か環境か」という古典的な二元論は大きな意味を持たない．多くの形質は遺伝要因と環境要因の交互作用で，その特定の表現型が表出するからである[4~6]．その点を理解したうえで，ある疾患において遺伝率を推定することは疾患感受性遺伝子探索の端緒として重要である．

図1　多因子性疾患に対する双生児研究法のアプローチ



双生児研究法の種々のアプローチ

双生児研究法はヒトゲノム計画の進展に呼応するかのように，この15年間で大きな変革を遂げた[2~3]．その要点を整理すると以下の3点となる．

① 統計遺伝学的解析手法の大幅な進歩

② 分子遺伝学的な解析手法との連動

③ ツインレジストリーをもとにした population－based な研究の推進

双生児研究法の種々のアプローチを図1に示した．端的に言えば，双生児を対象として，遺伝要因・環境要因・両者の関係を，マクロからミクロまで把握しうる強力なツールだということである．

1．統計遺伝学的解析手法の発展

量的遺伝学理論をもとにした古典的な遺伝率の推定理論に，共分散構造分析あるいは構造方程式モデリング（SEM）と呼ばれる統計解析手法を応用することで遺伝率解析は大幅に発展した．特に，統計解析ソフトの発達により，柔軟なモデルの構築が可能となり，複数の形質間の遺伝的関係を容易に推定できるようになった点が重要である．

メタボリックシンドロームを例に出すまでもなく，複数の多因子性疾患が併発することがある．分子レベルでの研究は容易でないが，双生児データに SEM を応用した多変量遺伝解析では，複数の形質に共通に関与する遺伝要因・環境要因，個々の形質に特異的に関与する遺伝要因・環境要因の寄与の割合を推定することが可能である（図２ａ）．得られた結果は，共通するリスク因子の推定のみでなく疾患関連遺伝子探索にも有効である．

多変量遺伝解析の応用として，双生児の縦断データを解析することで加齢や発達に伴う，遺伝要因と環境要因のダイナミックな挙動が把握でき，多因子性疾患の背景がより鮮明になる（図２ｂ）．

２．分子遺伝学的な解析手法との連動

DZ ペアは年齢の等しい同胞対であるから，疾患感受性遺伝子探索においても情報量が大きい．大規模な DZ サンプルを利用することで，連鎖解析の弱点であるペアの年齢差・環境差，関連分析の弱点である集団の層化などの影響を除いた妥当性の高い結果を得ることができる（図２ｃ，ｄ）．

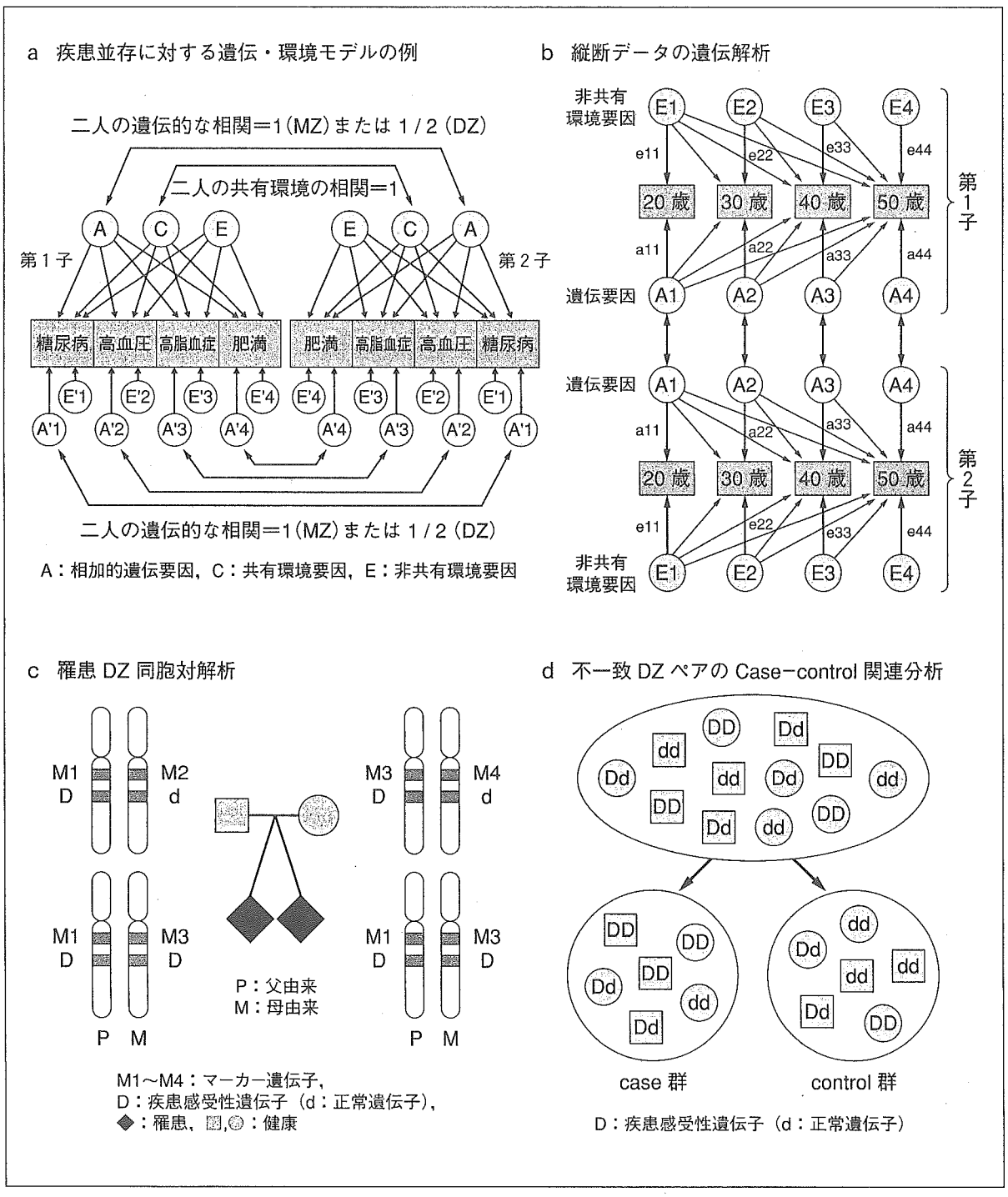
不一致 MZ ペアの遺伝子発現プロファイルあるいはエピジェネティックスの解析は，ゲノムが等しい個体における遺伝子機能の分子学的解明に寄与する．

DZ ペアは多因子性形質の量的遺伝子座（QTL）探索への応用にも寄与する．DZ ペアにおける同祖遺伝子情報を SEM に組み込むことで QTL の遺伝効果の推定値を高い妥当性で得ることができる．質的形質と同様な統計遺伝解析が量的形質にも可能となりつつある．また，量的遺伝学と分子遺伝学との大きなギャップも補完される可能性がある．

３．双生児を対象とした疫学研究

同性双生児を対象とした症例対照研究・コホート研究では，性・年齢の完全なマッチングがされている．また，観察項目以外の疾患条件，母体条件，環境曝露要因などが一般集団を対象とする以上に統制可能である．特に，MZ を対象とした環境要因研究は co－twin control study と呼ばれ，遺伝要因を完全に統制した状況での薬剤などの介入効果を測定できる．

図2　多変量遺伝解析のパス図（a，b）と疾患感受性遺伝子探索（c，d）



近年，インシュリン抵抗性ないし冠動脈疾患のリスクの1つとして胎内環境の中長期的影響が注目されている（胎児期環境仮説）．双生児は胎児期を同時に過ごす例外的な存在であり，母体要因を完全に統制して胎内環境曝露の影響を評価できる．

4．遺伝要因と環境要因のかかわり

現在の遺伝子医学の流れはともすれば遺伝子還元主義に傾きやすい．しかし，多因子性疾患は遺伝要因を背景としながらも現実にはさまざまな環境要因とのかかわりで発症する[4~6]．その間の交互作用を探索することは今後必須のステップとなる．双生児研究法は遺伝要因と環境要因のかかわりをマクロ・ミクロの両面から探索するうえでも有用である．不一致 DZ ペアの症例対象研究に疾患感受性遺伝子情報を組み込んだ解析はその一例である．一般に環境リスクの中には精度の高い測定が困難であるものも多いため，遺伝情報とのかかわりで評価することにより精緻な理解につながることが期待されている．双生児研究を用いれば遺伝学的な視点をも取り込んで環境要因の影響をより鮮明にすることが可能である．

ツインレジストリー

population－based な双生児データを用いることで，検出力の高い統計解析，妥当性の高い遺伝子探索が可能になる．多くの欧米先進国では遺伝疫学研究の資源として，数千～数万ペア単位でのツインレジストリーを構築している[7]．現在，欧州・豪州 8 ヵ国共同の Genom EUtwin 計画（http：//www.genomeutwin.org/）が EU の援助を受けた国際間プロジェクトとして進行中である．全体での対象双生児は実に 60 万ペアに上り，DNA 試料の蓄積も 1 万ペアに迫っている．

また，双生児を発端者とした家系のデータを系統的に収集することで情報量が飛躍的に上昇する（双生児家系研究）．

双生児研究法の限界

双生児研究法のメリットと同時にデメリットに関しても十分に検討する必要がある．まず，双生児から得られた結果の一般化の可能性の問題がある．問題とする形質に，表現型レベルで双生児と単胎児，MZ ペアと DZ ペアとの間で差が認められないことを確認する必要がある．また，分析対象の代表性ないしバイアスの評価も重要である．一般に，子宮内発育差の大きな双生児は対象から脱落しやすいとされる．さらに，双生児二人の子宮内環境は必ずしも同一ではない．特に，

MZ ペアの場合，胎盤卵膜所見の異なる3種類が存在するが，通常の双生児研究では産科的所見が得にくいためにこの点は考慮されにくい．生育環境に関しても MZ ペアと DZ ペアの類似度の確認（等環境仮説）が必要である．

以上の点を念頭に置いたうえでの結果の適切な評価が重要である．

双生児研究法の展望

双生児研究法は多因子性疾患発症において遺伝要因だけでなく環境要因の解明にも有用である．リスク因子の探索においては両者を区別する必要があっても，現実には遺伝要因を踏まえたうえでの環境要因のコントロールが多因子性疾患の予防には有効である．両者のかかわりを無視した予防は成立しえないことを強調しておきたい．

今後は，オーダーメイド医療と臨床疫学（EBM）的概念を包含した Evidence－based personalized disease prevention とでも言うべき巨視的な多因子性疾患の理解が有効となろう．その際，双生児研究法も有力な研究デザインの1つとして貢献することが期待される．

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Genetic and Environmental Etiology of Effortful Control

Shinji Yamagata,[1] Yusuke Takahashi,[1] Nobuhiko Kijima,[2] Hiroko Maekawa,[3] Yutaka Ono,[4] and Juko Ando[3]

[1] *Department of Cognitive and Behavioral Science, The University of Tokyo, Tokyo, Japan*
[2] *Psychological Laboratory, Keio University, Kanagawa, Japan*
[3] *Faculty of Letters, Keio University, Tokyo, Japan*
[4] *Health Center, Keio University, Kanagawa, Japan*

We examined whether effortful control (EC), a temperament proposed by Rothbart and Bates (1998), has genetically coherent structure. A self-report measure of EC was administered to 450 Japanese twins (151 males and 299 females, ages 17 to 32 years) including 152 monozygotic and 73 dizygotic pairs. Univariate genetic analysis revealed that AE model fit best for the total EC as well as its subscales. The heritability estimate for total EC was 49%, and the estimates for subscales ranged between 32% and 45%. Multivariate genetic analysis revealed that the subscales of EC were genetically correlated to a high degree and environmentally correlated to a moderate degree. These results suggest that EC has substantial genetic basis and genetically coherent structure, supporting the validity of the construct. The implications to molecular genetic study and study of psychopathology were discussed.

Since Ebstein et al. (1996) and Benjamin et al. (1996) reported the association between human personality and a genetic polymorphism, many researchers have been trying to investigate the molecular genetic basis of personality. Ebstein et al. (1996) and Benjamin et al. (1996) observed that individual differences in novelty seeking (Cloninger et al., 1993) were associated with a polymorphism of dopamine receptor D4 (DRD4). Further, Lesch et al. (1996) reported that harm avoidance (Cloninger et al., 1993) was associated with a polymorphism of the serotonin transporter long promoter region (5-HTTLPR). Increasing attempts to replicate the relationships yielded inconsistent results: some studies were successful (Murakami et al., 1999; Ono et al., 1997; Strobel et al., 1999; Tomitaka et al., 1999), whereas others were not (Gelernter et al., 1997; Kumakiri et al., 1999; Mitsuyasu et al., 2001). Finally, recent meta-analysis concluded that such associations were negligible (Kluger et al., 2002; Munafo et al., 2003; Schinka et al., 2002).

Several reasons contribute to the difficulty in obtaining the molecular genetic basis of personality. The first reason is small effect size of a single polymorphism. Even in studies that revealed a significant association, variance of a single polymorphism is typically 2% to 3%. This is because many polymorphisms exert influence on complex psychological traits like personality. Therefore, a typical sample size of 100 to 200 participants is sometimes not sufficient to detect such a small effect size. The second reason is sampling bias. For example, many studies use a psychiatric population as a sample, but having psychopathology may distort the subjects' self-report on personality, thereby obscuring the association between genes and personality. In addition, some associations between genes and personality may be specific to a certain age group, gender and culture. The third reason is the heterogeneity of the personality scale used. For example, anxious personality may be associated with the 5-HTTLPR polymorphism when measured with the Neuroticism scale of the Revised NEO Personality Inventory (NEO-PI-R; Costa & McCrae, 1992) but not when measured with the Harm Avoidance scale of the Temperament and Character Inventory (TCI; Cloninger et al., 1993). In fact, this conclusion was reached in a recent meta-analysis (Schinka et al., 2004; Sen et al., 2004). The reason why some scales are more related with certain polymorphisms may be due to (1) slight difference in the content they measure; or (2) low reliability, particularly low internal consistency. Given the high reliability of scales included in standard personality questionnaires such as NEO-PI-R and TCI, it is more plausible to consider that differences in the content, rather than reliability, are responsible for the inconsistent pattern of results.

However, the problem for association studies is that reliability is computed by phenotypic correlations among items or subscales, and not by the

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Address for correspondence: Shinji Yamagata, Department of Cognitive and Behavioral Science, Graduate School of Arts and Sciences, The University of Tokyo, Shigemasu Laboratory, 3-8-1 Komaba, Meguro-ku, Tokyo 153-8902, Japan. E-mail: yamagata@bayes.c.u-tokyo.ac.jp

genetic correlations among them. When subscales defining the same personality traits are phenotypically correlated with each other, the correlation may be due to genetic influence, environmental influence, or both. Thus, items or subscales defining the same trait may not share their etiology: some correlations among them may be due to genetic influences, whereas other correlations may be due to environmental influences. In fact, Ando et al. (2004) showed that a subscale of Novelty Seeking was genetically correlated to a greater extent with subscales of Harm Avoidance than with the other Novelty Seeking subscales. Although no one could predict the results beforehand, this genetic heterogeneity may be one of the reasons for the many inconsistent results of molecular genetic studies that examined the relationships between the DRD4 polymorphism and novelty seeking (Munafo et al., 2003). As such, computing genetic correlations and excluding genetically unrelated subscales or items makes genetically crisp categories (Faraone et al., 1999) and helps the association study by increasing the statistical power. Considering the fact that Cloninger's model is one of most accepted biological models of temperament, any temperamental traits that are theorized to have a specific genetic basis need to be empirically tested for genetic consistency before a molecular genetic study is conducted.

In this paper, we applied this approach to effortful control (EC), a temperament proposed by Rothbart et al. (2000). EC is a unique concept since it captures a self-regulative process that is rarely modeled by other personality theorists. EC is defined as 'the ability to inhibit a dominant response to perform a subdominant response' (Rothbart & Bates, 1998, p. 137) or the 'efficiency of executive attention, including the ability to inhibit a dominant response and/or to activate a subdominant response, to plan, and to detect errors' (Rothbart, personal communication, January 26, 2002, cited in Eisenberg et al., 2004). EC can be measured by questionnaires for various age groups ranging from infancy (3 to 12 months old; Rothbart, 1981), preschool and early school years (3 to 7 years old; Rothbart et al., 2001), early adolescence (9 to 15 years old; Ellis et al., 2004) to adulthood (Rothbart et al., 2000).

The reason why the genetic coherency of EC should be empirically tested is its importance in explaining psychopathology. As EC is in essence a measure of executive functioning, and as many experimental studies have shown that the lack of executive attention is found for various forms of psychopathology (Dobson & Dozois, 2004; Gotlib & Cane, 1987; Homack & Riccio, 2004; Mathews & Macleod, 1985; Sharma et al., 2001; Smith & Waterman, 2003), it is predicted that low EC should also be associated with them. In fact, empirical studies have shown that low EC is associated with both externalizing problems and internalizing problems (Eisenberg et al., 2001; Lemery et al., 2002; Oldehinkel et al., 2004). These findings suggest that low EC may be a common diathesis of both types of problems and explain high comorbidity between them. However, it could be also possible that EC consists of genetically heterogeneous subscales, and this heterogeneity enabled the scale to be associated with both externalizing and internalizing problems. In fact, a subscale of EC assessing control of inhibition tends to be associated more with externalizing problems, whereas another subscale assessing control of attention tends to be associated more with internalizing problems (Eisenberg et al., 2001). These two possibilities have very different implications for the field. If EC was shown to be genetically homogeneous, then the molecular genetic basis of EC should be rigorously examined as it can find the genetic risk factor common to both types of problems. Alternatively, if EC was shown to be genetically heterogeneous, then the reason for comorbidity between externalizing and internalizing problems should be explored elsewhere.

Thus, the current study was purported to examine whether EC is influenced by a homogeneous set of genes using Japanese adolescent and adult twin samples. This was done by first conducting univariate genetic analyses to show genetic influences on EC and its subscales, and then computing genetic and environmental correlations between the subscales.

Method

Participants

The questionnaire booklets were mailed to approximately 600 pairs of twins. All participants were volunteers in the Keio Twin Project (Ando & Ono, 1998), recruited via invitations sent to a population-based twin residential list of Tokyo and its neighboring cities. All subjects received written explanations of the purpose of the study, the research items, protection of their privacy, and their right to cancel their participation at any time if they wished. Subjects completed an informed consent agreement document. Subjects under 20 years of age were also required to obtain their parents' written consent. The final sample consisted of 225 pairs of twins, including 152 pairs of monozygotic (MZ) twins (104 female pairs and 48 male pairs) and 73 pairs of dizygotic (DZ) twins (34 female pairs, 16 male pairs and 23 opposite-sex pairs). The age range of the sample was 17 to 32 years (mean age = 24.15, *SD* = 4.28). Zygosity was determined using the questionnaire developed by Ooki et al. (1990). For a number of pairs, a clear zygosity diagnosis could not be made and their zygosity was determined on the basis of two gene polymorphisms (DRD4 and 5-HTTLPR) and genetic fingerprinting data. The accuracy of zygosity diagnosis is estimated to be between 91% and 95% in the present sample.

Instruments

The instrument used in the present study is the Japanese version of the Effortful Control scale

(Yamagata et al., in press). The EC scale for adults consists of three subscales: Activation Control (ACC), Attentional Control (ATC), and Inhibitory Control (IC). ACC measures the capacity to perform an action when there is a strong tendency to avoid it (e.g., 'I can make myself work on a difficult task even when I don't feel like trying'). ATC measures the capacity to focus attention as well as shift attention when desired (e.g., 'When interrupted or distracted, I usually can easily shift my attention back to whatever I was doing before'). Inhibitory Control measures capacity to suppress inappropriate approach behavior (e.g., 'When I decide to quit a habitual behavioral pattern that I believe to be undesirable, I am usually successful').

The Japanese version was developed through a back-translation procedure of the 35 original items of the Effortful Control scale included in the Adult Temperament Questionnaire (Rothbart et al., 2000). The Japanese version was reported to have good internal consistency (Cronbach's alpha = .90; for subscales, .74 to .84), test–retest reliability (r = .88; for subscales, r = .79 to .89; 3 weeks), and validity (positively correlate with the performance of the Stroop color-word interference task). Participants were asked to fill out the questionnaire with the instruction not to discuss or show their answers to their twin sibling.

Statistical Analysis

In order to assess the genetic and environmental contribution to phenotypic variations of EC and its subtraits, univariate genetic analyses, as described in Neale and Cardon (1992), were conducted with the computer program Mx (Neale et al., 1999). Univariate genetic analysis decomposes the similarities (covariances) of MZ and DZ twin pairs into estimates of additive genetic (A), nonadditive genetic (D), shared environmental (C) and nonshared environmental (E) influences. The effect of additive genetic factors (A) is assumed to be the sum of multiple genes (polygene) whose effects are small and additive to form a quantitative phenotype. The effect of nonadditive genetic factors (D) is assumed to be an interactive (nonadditive) contribution of alleles within a single locus (dominance). Shared environment (C) is the effect that makes family members alike not from heredity but from the common environment shared by all family members. Nonshared environment (E) is the effect that makes family members different even if they live together, such as physical illness and differential parental treatment. It also includes measurement errors.

In order to reveal which factors significantly contribute to phenotypic variances, four models were systematically compared in terms of goodness-of-fit statistics. These are the ACE model in which phenotypic covariances are explained by A, C and E; the ADE model explained by A, D and E; the AE model explained by just A and E; and the CE model explained by just C and E. Akaike's Information Criteria (AIC) was computed and used to determine the best model from these four. The AIC reflects a model's goodness of fit as well as its parsimony, and the model that results in the smallest AIC is regarded as the best. Parameter estimates for A, D, C and E are squared to compute the familiar proportions of the variance symbolized as h^2, d^2, c^2 and e^2.

Table 1

The Mean, SD, Range, and Intraclass Correlations of EC and Its Subscales

					Intraclass correlation	
	M	*SD*	Min.	Max.	MZ	DZ
EC	93.8	13.9	51	130	.45	.21
ACC	33.3	5.9	16	48	.38	.17
ATC	29.5	6.0	12	47	.42	.20
IC	31.0	4.9	14	44	.30	.12

Note: MZ = monozygotic twins; DZ = dizygotic twins; EC = Effortful Control; ACC = Activation Control, ATC = Attentional Control, IC = Inhibitory Control.

In order to compute the genetic and environmental correlations among EC subscales, multivariate genetic analyses were conducted. Multivariate genetic analysis is a model-fitting method to reveal genetic and environmental sources of phenotypic correlations. We first subjected the MZ and DZ within-pair covariances to a Cholesky decomposition using the Mx program as described in Neale and Cardon (1992). Specifically, we fit the AE Cholesky model to the twin covariances to estimate the additive genetic and nonshared environmental covariance matrices. We then converted the parameter estimates to the additive genetic (r_G) and nonshared environmental (r_E) correlations. For example, r_G between variables i and j was calculated from the genetic covariance between i and j (a_{ij}) and the genetic variance of i (a_{ii}) and j (a_{jj}) as such:

$$rG_{ij} = \frac{a_{ij}}{\sqrt{a_{ij} \times a_{ji}}}$$

The genetic and environmental correlations can be interpreted in the same way as any correlation coefficient: they vary from –1.0 to +1.0 to reflect the degree to which two variables are influenced by the same genetic or environmental factors.

Results

Descriptive Statistics

The mean, *SD*, range, and intraclass correlations for both MZ and DZ twins for EC and each of its subscales are shown in Table 1. For total EC as well as its subscales, intraclass correlations for MZ twins were higher than those of DZ twins, suggesting the existence of additive genetic influences.

Univariate Analysis

Table 2 shows the results of univariate genetic analyses of EC and its subscales. In terms of AIC, the AE model fit best for EC as well as its subscales. For the best-fitting AE model, additive genetic effects (h^2) explained 47% of phenotypic variance, whereas non-

Table 2

Results of Univariate Analyses

	model	χ^2	*df*	*p*	AIC	h^2	d^2	c^2	e^2
EC	CE	16.91	4	.00	8.91				
	ACE	8.93	3	.03	2.93				
	AE	8.93	4	.06	0.93	.49	—	—	.51
	ADE	8.42	3	.04	2.42				
ACC	CE	6.81	4	.15	−1.19				
	ACE	2.95	3	.40	−3.05				
	AE	2.95	4	.57	−5.05	.39	—	—	.61
	ADE	2.79	3	.43	−3.21				
ATC	CE	12.59	4	.01	4.59				
	ACE	6.65	3	.08	0.65				
	AE	6.65	4	.16	−1.36	.45	—	—	.55
	ADE	6.36	3	.10	0.36				
IC	CE	10.47	4	.03	2.47				
	ACE	7.18	3	.07	1.18				
	AE	7.18	4	.13	−0.82	.32	—	—	.68
	ADE	6.71	3	.08	0.71				

shared environmental effects (e^2) explained 53% of the variance. With regard to the subscales, heritability estimates ranged from .31 (Inhibitory Control) to .44 (Attentional Control).

Multivariate Analysis

Table 3 shows the genetic and environmental correlations among EC subscales. Correlations among the subscales were all positive in both the genetic and the environmental matrices. Genetic correlations were especially strong, with r_G ranging from .64 for between Activation Control and Inhibitory Control, to .93 for between Attentional Control and Inhibitory Control.

Discussion

This study examined the genetic and environmental etiology of EC using a Japanese adolescent and adult sample. Results of univariate analysis confirmed that EC as well as its subscales had a genetic basis. It is consistent with the finding of Goldsmith et al. (1997) that EC is heritable in childhood (h^2 = 58%). However, it is not surprising given the well-known fact that in adulthood, additive genetic and nonshared environmental effects account for variability in most personality traits (Bouchard & Loehlin, 2001).

The main focus of this study was rather on the genetic relationship between subscales of EC. As Ando et al. (2004) have recently shown in the case of Novelty Seeking, many temperaments were theorized for their genetic basis, but were in need of empirical examination for their genetic coherency. This was also the case for EC, but the multivariate analysis results in this study showed that subscales of EC were genetically correlated to a substantial degree. This suggests that individual differences in control with regard to activating and inhibiting behavior and attention are influenced by the same set of genes and form 'genetically crisp categories' (Faraone et al., 1999). Thus the EC scale can be readily used for the search of its molecular genetic basis. It also suggests that low EC is associated with both externalizing and internalizing problems because low EC can work as a common diathesis for the two types of problems, not because the scale contains genetic noise. Thus the molecular genetic study of EC is fruitful because it may reveal common genetic risk factors for internalizing and externalizing problems and contribute to their prevention.

Initially, the polymorphism of dopamine receptors and that of monoamine oxidase A (MAOA) may be good candidates. Derryberry and Rothbart (1997) and Rueda et al. (2004) proposed that individual differences in EC were founded on the activities of the anterior attentional system consisting of the anterior cingulate gyrus and the lateral prefrontal cortex that are modulated by dopamine. In fact, several neuroimaging studies revealed that tasks that require control of attention activate the anterior attentional

Table 3

Genetic and Environmental Correlations Among EC Subscales

	ACC	ATC	IC
ACC	—	.49	.34
ATC	.71	—	.31
IC	.64	.93	—

Note: Below diagonal: genetic correlations; above diagonal: environmental correlations.

network (Fan, Flombaum et al., 2003; Leung et al., 2000; Rubia et al., 2001), and that the amount of neural activation in anterior cingulate while the subjects performed the task was heritable (Fan et al., 2001) and associated with polymorphisms of the dopamine receptor gene and the MAOA gene (Fan, Fossella et al., 2003).

Testing genotype and environment (G × E) interaction in the development of EC is another direction for future research. Recently, Caspi et al. (2002) showed that aggressive behavior and conduct problems, which are closely related to low EC (Eisenberg et al., 2000; Ellis et al., 2004) were explained by the interaction between a polymorphism of the MAOA gene and parental maltreatment. It could be possible that this interaction accounts for individual differences in EC, and EC mediates the relationship between the G × E interaction and aggressive behavior.

Finally, some methodological limitations should be noted. First, it is unclear whether the present results can be applied to cultures outside Japan. Rothbart et al. (2001) reported that in children, the structure of EC differed in China, Japan and the United States. Thus, in cultures other than Japan, the etiology of EC in adulthood may be different. Further, the sample size of the present study was not sufficient to examine gender-specific effects. Olson et al. (1990) reported that the relationship between behavioral measures of EC and parenting differs depending on gender. Hence, it is necessary to examine gender-specific effects using a larger sample.

In conclusion, the results of the present study indicate that EC is genetically influenced to a substantial degree and has a genetically coherent structure. These results support the validity of the construct from a genetic point of view and encourage the search for a molecular genetic basis of temperament as a common diathesis for both internalizing and externalizing problems.

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Short Communication

Local community intervention through depression screening and group activity for elderly suicide prevention

HIROFUMI OYAMA, MD, PhD,[1] YUTAKA ONO, MD, PhD,[2] NAOKI WATANABE, MD, PhD,[3] ERIKO TANAKA, MA,[4] SEIJIRO KUDOH, MD,[5] TOMOE SAKASHITA, MA,[6] SHINJI SAKAMOTO, PhD,[7] KEIKO NEICHI,[8] KYOKO SATOH,[8] KENJI NAKAMURA, MD, PhD[9] AND KIMIO YOSHIMURA, MD, PhD[10]

[1]*Department of Social Welfare, Aomori University of Health and Welfare, Aomori,* [2]*Health Center, Keio University, Yokohama,* [3]*Aomori Prefecture Mental Health and Welfare Center, Aomori,* [4]*Working Life Conditions and Welfare Support Research Group, The Institute for Science of Labour, Kawasaki,* [5]*Department of Psychiatry, Seisyokai Minato Hospital, Hachinohe,* [6]*Faculty of Social Welfare, Iwate Prefectural University, Takizawa,* [7]*Department of Psychology, Nihon University, Tokyo,* [8]*Division of Health and Welfare, Nagawa Town Office, Nagawa,* [9]*Department of Human and Welfare for Persons with Disabilities, Ministry of Health, Labour and Welfare, Tokyo, and* [10]*Center Information and Epidemiology Division, National Cancer Center Research Institute, Tokyo, Japan*

Abstract This study aims to evaluate outcomes of a community-based program to prevent suicide among the elderly (≥65 years old) using a quasi-experimental design with two neighboring references. During 1999–2004, the program including depression screening and group activity was conducted by the public health nurses in the Minami district (population 1685) of Nagawa town, rural Japan. Pre-post changes in the risk of completing suicide were estimated by the incidence rate ratios (IRR). The risk for Minami's elderly females was reduced by 74% (age-adjusted IRR, 0.26; 90% CI, 0.07–0.98) more than the historical trend, while there was no change in the risk of Minami's males and nor in the male or female references. The local intervention using public health nursing would be effective against suicide for elderly females without diffusing to the surroundings.

Key words community-based intervention, depression screening, elderly, gender difference, suicide prevention.

INTRODUCTION

The high prevalence of suicide among the elderly is a major social problem in Japan. There is also a regional difference in the elderly suicide rate, with agricultural areas having a higher rate than urban areas. Recent studies demonstrate that depression is the strongest risk factor for late-life suicide.[1] Although few previous interventions in Japan have resulted in reducing the suicide rate in the elderly, most of them used screening for depression in the rural community.[2,3]

We have developed a community-based program, SUPPRESS, the details of which have been described previously.[4,5] The intervention program included three components: (i) two-stepped screening for depression (using five self-reported items[6] in the first step and a mental health assessment by the trained public health nurses [PHN] in the second step, once a year) and follow-up by PHN; (ii) mental health workshop (psychoeducational program, providing the information regarding depression, 3–4 times a year); and (iii) a group activity program (participating in social, voluntary and recreational activities and exercising, once a

Correspondence address: Hirofumi Oyama, MD, PhD, Department of Social Welfare, Aomori University of Health and Welfare, 58-1 Mase Hamadate, Aomori 030-8505, Japan.
Email: h_oyama@auhw.ac.jp

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month). Since 1999, the program was implemented in the Minami district of Nagawa town. The aim of the present study was to evaluate the effectiveness of this program for the prevention of elderly suicide using a quasi-experimental design with neighboring references.

METHODS

Study population and design

The study terms were divided into two 6-year stages: the baseline set before the initiation in January 1993–December 1998 and the implementation after that in January 1999–December 2004. The study population (≥65 years old) consisted of three identical dynamic cohorts in 1993–2004, an intervention cohort and two reference cohorts. The intervention cohort was made up of the population in Minami district (total population 1685, elderly percentage 25.3% in 1998; average suicide rate [≥65 years old] 403.6/10^5 in the baseline stage) of Nagawa town, in Sannohe county of northern Japan. The town is located in an agricultural rural area with a high suicide rate.

The municipalities in Sannohe county were eligible as study references with the following criteria: (i) population ≤ 10 000; (2) elderly percentage ≥ 20%; and (3) average suicide rate ≥ 150/10^5. Of those, only Shingou village (population 3300, elderly percentage 30.5% in 1998, average suicide rate [≥65 years old] 161.7/10^5 in the baseline) fulfilled the criteria without implementation of depression screening and entered as a neighboring reference (Shingou's reference cohort). The village is located in an agricultural rural area, 6 km geographically west of Nagawa. Another reference cohort was made up of the Nagawa population (≥65 years old) except those in Minami district (Nagawa's reference cohort).

The data on suicide was derived from prospective registration of all suicide episodes at Hachinohe Public Health Center. The diagnoses in the register were based on ICD-9, in which confirmed suicides and probable suicides were treated together.

Statistical analysis

Statistical analysis was based on an incidence rate (IR) of completed suicide with stratification for age and gender, which is the number of incident suicide cases divided by the population-years. The incident suicide cases and annual populations were derived from the dynamic cohort during each 6-year stage.

Changes in the risk of completing suicide associated with the factor 'exposure to the community program' were expressed as the IR ratio (IRR) between the baseline and implementation stages. This is because the risk ratio (RR) was interchangeable with the IRR under (i) the assumption of constancy of the IR over each stage; and (ii) the rarity of suicide (the IR less than 0.5%).[7] The IRR of the population aged 65 and over between the two stages were assessed using a Mantel–Haenszel (M-H) stratified χ^2 test adjusted for 10-year age categories with maximum likelihood method estimates. The homogeneity of the IRR in age levels was also assessed by a Breslow–Day test. Furthermore, the analysis compared the crude IRR in the intervention area with that in the reference of the same town for evaluation of the effect of a regional historical trend. A three-factor interaction parameter obtained from a saturated general loglinear model for a $2 \times 2 \times 2$ cross-classification was calculated using the maximum likelihood estimation with χ^2 test (d.f. = 1) for comparison. This parameter expresses a ratio of two IRRs.[8]

Since there was an explicit hypothesis stating that the intervention should have a beneficial, if any, impact, 90% confidence intervals (CI) can be legitimately used. Descriptive statistics and CI were calculated using the SPSS 11.0 J software package (SPSS Inc., Chicago, IL, USA).

RESULTS

Implementation of the intervention program

The workshops for psychoeducation were held together with the group activity programs in the intervention area. The number of those who participated in the activity program at least once a year increased from 43 (seven males and 36 females) to 106 (16 males and 90 females) in the implementation. Approximately one-third of the elderly females and one-tenth of the males took part in the educational, social activity program in recent years.

Table 1 shows the range of numbers of participants in the annual two-stepped screening and follow-up. Unfortunately, we could not count the exact number of participants in the first step screening since the written questionnaires were shredded immediately after scoring in order to protect privacy. Thus, we estimated that more than 60% male and 80% female residents aged 65 and over participated in the first step. Of the participants, approximately 20–29% males and 30–39% females were enrolled as positive. For females, the annual numbers of participants who were enrolled as positive in the second step screening and those who received the follow-up were larger than for males during the implementation.

Table 1. Range of annual numbers of participants in the two stepped-screening and follow-up during the implementation stage (1999–2004) in the intervention area (Minami district)

Program item	Males	Females
Population aged 65 and over	165–182	238–282
First step screening		
Participants (%)	60–89*	80–95*
Positive (%)	20–29*	30–39*
Second step screening		
Participants	28–42	62–88
Positive	5–16	22–35
Follow-up		
PHN's follow-up interview	1–3	4–6
Referral to a psychiatrist	0–1	0–2

*Approximation of a percentage.

Change in incidence rates of suicide in the study population

Of four suicide victims in the implementation, two (one male and one female) had been enrolled as negative in the first step screening. The other two victims (one male and one female) had not participated in the intervention programs.

Table 2 shows the number of suicides and person-years aged 65 and over for each 6-year stage and the results of the M-H test. In the intervention area, a 74% reduced risk for females aged 65 and over was observed (age-adjusted IRR, 0.26; 90% CI, 0.07–0.98) during the implementation, compared with the baseline. There was no significant change in the risks for its males and nor for males or females in two references before and after the implementation.

General loglinear analysis for cell degrees added 0.5 because of the less than 5-degree estimated for a ratio of the crude IRR among the elderly females [(2/1598)/(5/1173)] in the intervention area to that [(11/7778)/(5/6580)] in Nagawa's reference of 0.19 (90% CI, 0.04–0.86). This means that a reduction of the female RR in the intervention area was greater than that in the same town (i.e. the regional historical trend).

DISCUSSION

Although it is widely known that most of the elderly people who commit suicide are suffering depression immediately before,[9,10] there are few effective interventions proven to reduce suicidal behavior in senior adults.[11] In the present study, a program focussing on detection and management of depression, SUPRRESS, was prospectively evaluated by the outcome from demographic data observed by public organizations. The suicide risk for elderly females, but not males, in the intervention population was reduced by 74% during the 6-year implementation. Of the present results, the reduced risk for females is localized in the intervention population as well as the two previous results; in contrast to the unchanged risk for males.[2,3]

The present findings suggest that the interventions were effective in reducing suicide risk among the elderly females unless some biases resulting from this quasi-experimental design could significantly affect the risk. Since the present study adopted a before-and-after design with non-randomized references, the following biases could result. First, non-randomized assignment cannot control unmeasured confounding variables. However, for the variables related to suicide, the socioeconomic background including unemployment rates, average yearly income and welfare service appears to be similar between the intervention and references because of the neighborhood and the belonging to the same county. Second, the before-and-after design could cause time-dependent confounding, including a historical trend, and a regression effect towards the mean. Nevertheless, the female reduction of suicide risk in the intervention area was greater than the regional historical trend. A regression effect on the decrease of the suicide rate in the intervention area could also be suspected because of the high baseline rate. However, the elderly suicide rates in the neighboring references were continuously high. This counters an explanation of the regression effect.

A gender difference of the risk changes following the implementation can be explained by (i) accepting more females than males; and (ii) lack of psychiatric care ameliorating the suicidal impulse to which males would be more vulnerable than females.[12] The effect of depression screening implemented by the present and two previous interventions would also not diffuse to the surrounding areas.

The present study cannot clarify whether the reduction of the female suicide risk is attributable to the depression screening or the group activity program with psychoeducation. There were substantial numbers of the present female participants in both screening and group activity program. Since the previous community interventions have resulted in reducing the suicide risk among elderly females using depression screening[3] or group activity and psychoeducation,[12] either program may cause the female reduction.

The present study has limitations. First, the small sample size could cause unsuccessful detection of the risk changes. Second, we were unable to control all potential confounders. Nevertheless, there are indications that the reduction by depression screening and

Table 2. Change in incidence rates (IR) of suicide before and after the implementation in the study areas, displayed by age and gender

Subject	Age (years)	Baseline (January 1993–December 1998)		Implementation (January 1999–December 2004)		Breslow-Day test			Mantel-Haenszel test				
												Age-adjusted IR ratio	
		n	Person-years	*n*	Person-years	χ^2	d.f.	*P*-value	χ^2	d.f.	*P*-value	Estimate	90% CI
Males													
Intervention area													
Minami district*	65–74	2	550	0	628	1.85	1	0.17	0.62	1	0.43	0.48	0.10–2.31
	75–84	1	219	2	329								
	85+	0	40	0	79								
Reference													
Nagawa's reference†	65–74	4	3125	4	3439	0.94	1	0.33	0.72	1	0.40	0.61	0.24–1.59
	75–84	3	1246	1	1642								
	85+	0	237	0	308								
Shingo's reference	65–74	2	1590	3	1663	1.51	2	0.47	0.21	1	0.65	0.75	0.27–2.10
	75–84	2	467	2	881								
	85+	1	125	0	145								
Females													
Intervention area													
Minami district*	65–74	1	754	1	837	1.80	2	0.46	3.20	1	0.07	0.26	0.07–0.98
	75–84	2	338	0	610								
	85+	2	81	1	151								
Reference													
Nagawa's reference†	65–74	3	4131	5	4183	0.38	2	0.83	1.26	1	0.26	1.83	0.75–4.48
	75–84	2	1947	5	2822								
	85+	0	502	1	773								
Shingo's reference	65–74	3	1853	1	1920	1.77	1	0.18	0.02	1	0.89	0.91	0.28–2.96
	75–84	1	1152	3	1343								
	85+	0	379	0	567								

*Exposed cohort area in Nagawa town.
†Nagawa town except Minami district.

group activity with psychoeducation was successful for elderly females.

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Regular Article

The development of a brief screening instrument for depression and suicidal ideation for elderly: the Depression and Suicide Screen

DAISUKE FUJISAWA, MD,[1] ERIKO TANAKA, MA,[2] SHINJI SAKAMOTO, PhD,[3] KEIKO NEICHI, RN PHN,[4] ATSUO NAKAGAWA, MD[5] AND YUTAKA ONO, MD[6]

[1]*Division of Psychiatry, Sakuragaoka Memorial Hospital, Tokyo,* [2]*Working Life Conditions and Welfare Research Group, The Institute for Science of Labor, Kawasaki,* [3]*Department of Psychology, Nihon University, Tokyo,* [4]*Division of Health and Welfare, Nagawa Town Office, Aomori, Japan,* [5]*Department of Psychiatry, Division of Neuroscience, Columbia University, New York, USA,* [6]*Stress Management Division, Keio University School of Medicine, Tokyo, Japan*

Abstract The early detection of depression and suicidal ideation is essential for the prevention of suicide in the community. This study therefore aimed to develop a brief screen for depression and suicidal ideation that can be easily administered in primary-care settings. The Self-rating Depression Scale (SDS), the Hospital Anxiety and Depression Scale (HADS) and a modified version of the Composite International Diagnostic Interview (CIDI) were administered by 353 residents of a single community aged 64 years and over. A five-item screen was derived from SDS and HADS, using CIDI as the external criterion (study 1). The scale was modified so that it was more appropriate for our use, and was labeled the Depression and Suicide Screen (DSS). Its validity and reliability were examined among a further 382 residents of the same community aged 64 years and over, using the Short-Form Geriatric Depression Scale (GDS-S) as the external criterion (study 2). The DSS was internally consistent (Cronbach's alpha = 0.62). Its reliability in detecting depression (defined as ≥ 6 in GDS-S) and suicidal ideation (screened out by the inquiry by our trained staff) was 0.768 and 0.721, respectively. For depression, the sensitivity was 0.705; specificity, 0.729; positive predictive value (PPV), 0.446; negative predictive value (NPV), 0.888; and the overall diagnostic power, 0.723. For suicidal ideation, its sensitivity was 0.698; specificity, 0.693; PPV, 0.317; NPV, 0.926; and overall diagnostic power, 0.694. The DSS demonstrated a reasonable level of sensitivity and specificity in identifying both depression and suicidal ideation among the elderly within a community.

Key words community mental health, elderly, depression, suicide prevention, screening.

INTRODUCTION

The number of suicides in Japan has been increasing, with the largest portion occurring among the elderly. Psychiatric autopsies have demonstrated that major depression is the leading cause of suicide in later life.[1] It has been reported that mild or 'subthreshold' depression, if left untreated, increases the risk of suicide.[2] Therefore, as a suicide prevention strategy, it is essential to detect depression in its early stages.[3–5] However, there are several barriers to the early detection of depression in primary care. First, people in the community are not necessarily familiar with mental disorders, or they may have a negative prejudice against mental disorders, and are therefore unlikely to consult mental health professionals. Second, health workers in the community may not be familiar with mental disorders such as depression. Many physicians and other primary care providers believe that depression is a normal part of aging,[6] and they may miss the diagnosis of late-life depression because of insufficient training, or because of their focus on medical conditions that mask the presence of depression. Third, time

Correspondence address: Daisuke Fujisawa, MD, Division of Psychiatry, Sakuragaoka Memorial Hospital, 1-1-1 Renko-ji, Tama-shi, Tokyo, Japan. Email: fujisawa@sc.itc.keio.ac.jp

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