Regular Article

Association between Selective Serotonin Reuptake Inhibitor Therapy and Suicidality: Analysis of U.S. Food and Drug Administration Adverse Event Reporting System Data

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Selective serotonin reuptake inhibitors (SSRIs) are prescribed for the treatment of depression worldwide. SSRIs are suspected to increase the risk of suicidal ideation and behavior (suicidality) in children, adolescents, and young adults. We examined the association between SSRI therapy and suicidality by applying a logistic regression model to age-stratified data from the Food and Drug Administration (FDA) Adverse Event Reporting System database. We attempted to mitigate the effect of patient-related factors by data subsetting. We selected case reports for SSRIs as referred to in the World Health Organization Anatomical Therapeutic Chemical classification code N06AB. The association between SSRIs and "suicidal events" or "self-harm events" was calculated as a reporting odds ratio (ROR) and adjusted for covariates by logistic regression. For subjects <18 years old (y.o.) the adjusted RORs (95% confidence interval) of SSRI therapy with suicidal events were 9.58 (8.97–10.23) in the whole data analysis and 4.64 (4.15–5.19) in the subset analysis; those with self-harm events were 31.40 (27.71–35.58) and 16.31 (13.12–20.29), respectively. Although the adjusted RORs were lower in the subset analyses than in the whole data analyses, both analyses indicated associations between SSRI treatment and suicidal and self-harm events. In both analyses these associations were stronger in the <18 y.o. group than other age groups. Children and adolescents should be closely monitored for the occurrence of suicidality when they are prescribed SSRIs. In addition, we found that data subsetting might mitigate the effect of an intrinsic risk among patients taking the suspected drug.

Key words selective serotonin reuptake inhibitor (SSRI); suicidality; adverse event; reporting odds ratio (ROR)

Selective serotonin reuptake inhibitors (SSRIs) are prescribed for the treatment of depression worldwide.[1] Several studies including clinical,[2–5] an observational,[6] meta-analyses[7,8] and a systematic review[9] suggest that SSRIs increase the risk of a suicide attempt, suicidal behavior, and suicidal ideation or self-harm events, or both. In December 2006, the Psychopharmacologic Drug Advisory Committee of the U.S. Food and Drug Administration (FDA) released a report on the risk of suicidal thinking and behavior in patients administered antidepressants.[10] This report stated that (1) young adults aged 18–24 years have a potentially increased suicide risk during initial the drug treatment, (2) the increased risk was not supported by scientific data in persons older than 24 years, and (3) adults aged 65 years and older administered antidepressants have a decreased suicide risk.[10] In May 2007, the FDA announced that SSRIs might increase the risk of suicidal thinking and behavior in young adults aged 18–24 years during the initial drug treatment period and, consequently, SSRI product labels were updated.[11] In several studies, antidepressant drug treatment was significantly associated with suicide attempts, self-harm, or both in children and adolescents (aged 6–18 years).[2–5,8,9] Another observational study indicated that SSRIs prescriptions were associated with a decreased suicide rate in young adolescents.[12] The previous findings on SSRI use and suicide do not allow us to determine confidently whether this safety issue can be stratified by patient age.

The FDA Adverse Event Reporting System (FAERS) is one of the largest Spontaneous Reporting Systems (SRSs) used for pharmacovigilance and contains several million case reports on adverse events. Several pharmacovigilance indexes were developed to detect drug-associated adverse events in SRSs, including the reporting odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), and empirical Bayes geometric mean (EBGM), which are widely used.[13] The PRR is currently used by the Medicines and Healthcare Products Regulatory Agency in the United Kingdom (U.K.), the ROR by the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the Netherlands Pharmacovigilance Centre (Lareb), the IC by the World Health Organization (WHO), and the EBGM by the FDA. The ROR is a clear, inexpensive, easy to understand, and applicable technique, which allows the control of covariates through logistic regression analysis and can be used to analyze the use of interaction terms in detail.[14–16]

Furthermore, subset analysis, which mitigates bias and the influence of confounding variables, can be applied in the evaluatation of drug-adverse event associations in disproportionality analyses using the ROR.[17–19]

To the best of our knowledge, the relationship between SSRI and suicidality has not yet been evaluated in terms of age-stratified patient groups from the FAERS database. In this study, we evaluated the possible relationship between SSRI use and suicidality from data available in the FAERS database using a logistic regression model and subset analysis, and

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obtained information regarding confounding factors from the reported cases such as age, sex, and drug use. Furthermore, the relationship between non-selective monoamine reuptake inhibitors (NSRIs) including tricyclic antidepressants (TCAs) and suicidality was also evaluated and compared with the result of the SSRIs.

MATERIALS AND METHODS

Data Source The FAERS database is the largest and best-known database of adverse events, and it reflects the realities of clinical practice. As a result, the FAERS database is one of the primary tools used in pharmacovigilance. Adverse events records from January 2004 to June 2014 were obtained from the FDA web site. FAERS consists of 7 data tables: patient demographic and administrative information (DEMO), drug/biological information (DRUG), adverse events (REAC), patient outcomes (OUTC), report sources (RPSP), drug therapy start and end dates (THER), and indications for use/diagnosis (INDI). In the DRUG table of FAERS, administered drugs are recorded using their generic or brand name. DrugBank,[20–23] a reliable drug database, was used as a reference source for the batch conversion and compilation of the trivial and generic drug names. Following the FDA's recommendations, we excluded duplicate reports of the same patient from different reporting sources from the analysis and extracted reports that were complete with age and sex information.

Data Subsetting The data subsetting strategy may help to mitigate the effect of confounding factors on signal detection by limiting the analysis to a population of patients that are thought to share common risk factors and diseases.[17–19] Because depression is one of the risk factors associated with suicidality,[24] we evaluated the intraclass RORs of the *depression patient* subset. For the calculation of the intraclass ROR, we defined a subset of depressed patients from the whole FAERS data. The records were subsetted by the term "depression" as found in the INDI table. The subset data consisted of records, including "depression" or "major depression." The term "major depressive disorder" was not present in the INDI table. When the indication field in the INDI table was not completed, the record was excluded from the subset data. Because the FAERS database does not contain information on the severity of depression, this information was not taken into account in this analysis.

Study Drugs and Definition of Adverse Events We selected case reports for SSRIs and NSRIs as described in the WHO Anatomical Therapeutic Chemical classification code N06AB (SSRIs) and N06AA (NSRIs).

The adverse events in the REAC are coded according to the terminology preferred by the Medical Dictionary of Regulatory Activity (MedDRA) 17.1. The cases of "suicidal events" include one or more of the following preferred terms (PTs): PT10010144 (completed suicide), PT10042458 (suicidal ideation), PT10042464 (suicide attempt), and PT10065604 (suicidal behavior). Cases of "self-harm events" include PT10022524 (intentional self-injury), PT10051154 (self-injurious ideation), and PT10063495 (self-injurious behavior). Non-cases consisted of patients associated with all other reports.

Stratification of Cases According to the recommendation of the FDA's Psychopharmacologic Drug Advisory Committee in December 2006,[10] the records were stratified according to the age of the patient (<18, 18–24, 25–64, and ≥65-years-old [y.o.]).

Statistical Analysis Several reports on pharmacovigilance have recently discussed the use of ROR as a measure of disproportionality.[17,25–28] In the present study, the association between SSRIs and suicidal or self-harm events was calculated as an ROR. The RORs were calculated from two-by-two contingency tables of counts that indicated the presence or absence of a particular drug and a particular adverse event in the case reports, and were expressed as point estimates with 95% confidence intervals (CIs). The safety signal was defined as the lower limit of the 95% CI for an adjusted ROR exceeding one.[28]

The ROR can be adjusted using logistic regression analysis,[25,26] which offers the possibility of controlling for covariates, and can be used to analyze the effects of the interaction terms in detail.[25–27] We applied the logistic regression model in the calculation of adjusted RORs for age-stratified patient data and refined the safety signal with a dedicated correction to detect possible confounding factors present in the database. The RORs were adjusted for gender, reporting year, and stratified age group by applying logistic regression analysis. To construct the logistic model, drug (SSRIs or NSRIs) and the co-occurrence of drugs and the age-stratified groups were coded. The following logistic model was used for the analysis:

$$\log(\text{odds}) = \text{intercept} + b1G + b2Y + b3D + b4A + b5D*A$$

where G=gender, Y=reporting year, D=drug (SSRIs or NSRIs), and A=age-stratified group.

The 25–64 y.o. group was used as a reference in calculating the adjusted RORs. A likelihood ratio test can be used to evaluate the effect of adding a particular term. Because the difference in −2 log-likelihood follows a chi-square distribution with 1 degree of freedom, adding the interaction term, in this case, was statistically significant ($p<0.05$). Data analyses were performed using the JMP 11.0 (SAS Institute Inc., Cary, NC, U.S.A.).

RESULTS

SSRIs

Suicidal Events Related to SSRIs The characteristics of the cases and non-cases of the whole and subset data are summarized in Tables 1 and 2, respectively. The whole data from FAERS contained 5821354 reports from January 2004 to June 2014. After the exclusion of duplicates and extraction of reports that included age and sex, 2892258 reports were analyzed. The number of suicidal event reports was 58597 (Table 1). The subset of patients who were depressed including their age and sex was described in 97501 reports (Table 2). The number of reports of suicidal events in the subset data was 8320 (Table 2).

The adjusted RORs and 95% CIs for the whole and subset data are summarized in Tables 3 and 4. We calculated the adjusted ROR for each stratified category. The adjusted RORs (95% CI) of the SSRIs for the whole and subset data were 4.45 (95% CI, 4.35–4.56) and 1.42 (95% CI, 1.34–1.49), respectively. The adjusted RORs (95% CI) of male patients for the whole and subset data were 1.37 (95% CI, 1.35–1.40) and 1.50 (95% CI, 1.43–1.57), respectively. The effect of the SSRIs

term in the likelihood ratio test (chi-square test, $p<0.0001$) and the interaction term for SSRIs in the <18 y.o. group in the whole and subset data were both statistically significant (Tables 3, 4). Although the interaction term for the SSRIs in the ≥65 y.o. group for suicidal events was statistically significant according to the likelihood ratio test ($p<0.0001$) for the whole data (Table 3) but not subset data ($p=0.2030$) (Table 4). The adjusted RORs for the patients were stratified per age group, using the 25–64 y.o. patients as a reference group. The adjusted RORs of the 18–24 y.o. patients for the whole and subset data were 1.79 (95% CI, 1.73–1.84) and 1.89 (95% CI, 1.65–2.15), respectively. The effect of the interaction term for the SSRIs in the <18 y.o. group (b5D*A) was statistically significant ($p<0.0001$) and the adjusted RORs for the SSRIs for the whole and subset data in this group were 9.58 (95% CI, 8.97–10.23) and 4.64 (95% CI, 4.15–5.19), respectively. The adjusted ROR for the SSRIs in the ≥65 y.o. group for the whole data was 1.25 (95% CI, 1.18–1.33). In the subset analy-

Table 1. Demographic Data of Patient for Analysis of Whole Data

	Cases	Non-cases	Total	Crude ROR (95% CI)
Suicidal events[a)]				
Total	58597	2833661	2892258	—
Male	25883	1099896	1125779	1.25 (1.23–1.27)
Age (y.o.)				
<18	4932	146264	151196	1.69 (1.64–1.74)
18–24	5451	119530	124981	2.33 (2.26–2.40)
25–64	42853	1666613	1709466	1.91 (1.87–1.94)
≥65	5361	901254	906615	0.22 (0.21–0.22)
SSRIs	13277	158535	171812	4.94 (4.85–5.04)
NSRIs	2918	36827	39745	3.98 (3.83–4.14)
Self-harm events[b)]				
Total	5379	2886879	2892258	—
Male	2273	1123506	1125779	1.15 (1.09–1.21)
Age (y.o.)				
<18	1104	150092	151196	4.71 (4.41–5.03)
18–24	731	124250	124981	3.50 (3.23–3.78)
25–64	3263	1706203	1709466	1.07 (1.01–1.13)
≥65	281	906334	906615	0.12 (0.11–0.14)
SSRIs	1469	170343	171812	5.99 (5.64–6.36)
NSRIs	184	39561	39745	2.55 (2.20–2.95)

a) It consisted of 4 PTs; "complete suicide," "suicidal ideation," "suicide attempt," and "suicidal behavior." *b*) It consisted of 3 PTs; "intentional self-injury," "self-injurious ideation," and "self-injurious behavior."

Table 2. Demographic Data of Patient for Analysis of Subset Data

	Cases	Non-cases	Total	Crude ROR (95% CI)
Suicidal events[a)]				
Total	8320	89181	97501	—
Male	3277	26452	29729	1.54 (1.47–1.61)
Age (y.o.)				
<18	666	2029	2695	3.74 (3.41–4.09)
18–24	721	3895	4616	2.08 (1.91–2.26)
25–64	6256	64156	70412	1.18 (1.12–1.25)
≥65	677	19101	19778	0.32 (0.30–0.35)
SSRIs	4721	42046	46767	1.47 (1.41–1.54)
NSRIs	512	5274	5786	1.04 (0.95–1.15)
Self-harm events[b)]				
Total	882	96619	97501	—
Male	288	29441	29729	1.11 (0.96–1.27)
Age (y.o.)				
<18	170	2525	2695	8.90 (7.49–10.57)
18–24	157	4459	4616	4.48 (3.76–5.33)
25–64	520	69892	70412	0.55 (0.48–0.63)
≥65	35	19743	19778	0.16 (0.11–0.23)
SSRIs	592	46175	46767	2.33 (1.94–2.57)
NSRIs	66	5720	5786	1.29 (0.99–1.65)

a) It consisted of 4 PTs; "complete suicide," "suicidal ideation," "suicide attempt," and "suicidal behavior." *b*) It consisted of 3 PTs; "intentional self-injury," "self-injurious ideation," and "self-injurious behavior."

sis, there was no interaction between the SSRIs in this age group ($p=0.2030$).

Self-harm Events Related to SSRIs The whole and subset data contained 5379 and 882 reports of "self-harm events," respectively (Tables 1, 2).

The adjusted RORs (95% CI) of the SSRIs for the whole and subset data were 5.27 (95% CI, 4.88–5.70) and 1.71 (95% CI, 1.44–2.04), respectively. The effects of the term "SSRIs" were statistically significant in the likelihood ratio test ($p<0.0001$) (Tables 3, 4). The adjusted RORs of patients <18 y.o. for the whole and the subset data were 3.70 (95% CI, 3.41–4.01) and 4.16 (95% CI, 2.62–6.29), respectively (Tables 3, 4). The effect of the interaction term for the SSRIs in the <18 y.o. group (b5D*A) for the subset data was statistically significant ($p=0.0003$). The RORs for the SSRIs in the <18 y.o. patients for the whole and subset data were 31.40 (95% CI, 27.71–35.58) and 16.31 (95% CI, 13.12–20.29), respectively. The interaction terms of the SSRIs in the ≥65 y.o. group for the whole and subset data were not statistically significant.

NSRIs

Suicidal Events Related to NSRIs The adjusted RORs and 95% CIs for the whole and subset data are summarized in Tables 5, 6. The adjusted ROR (95% CI) of the NSRIs for subset data was 1.05 (95% CI, 0.95–1.17). The effect of the term "NSRIs" for suicidal events was statistically significant according to the likelihood ratio test ($p<0.0001$) in the whole (Table 5) but not subset data ($p=0.3386$, b3D, Table 6).

The adjusted ROR of the <18 y.o. patients for the subset data was 2.99 (95% CI, 2.72–3.29). The effect of the interaction term for the NSRIs in the <18 y.o. group (b5D*A) was statistically significant ($p=0.0010$) and the adjusted ROR was 7.34 (95% CI, 4.60–11.72).

Self-harm Events Related to NSRIs The adjusted ROR (95% CI) of the NSRIs for the subset data was 1.29 (95% CI, 0.92–1.77). The effect of the term "NSRI" for the self-harm events was statistically significant according to the likelihood ratio test ($p<0.0001$) for the whole (Table 5) but not subset data ($p=0.1404$, b3D, Table 6).

The adjusted ROR of the <18 y.o. patients for the subset data was 8.92 (95% CI, 7.41–10.69). The effect of the interaction term for the NSRIs in the <18 y.o. group (b5D*A) was not statistically significant ($p=0.7573$) and the adjusted ROR was 9.90 (95% CI, 3.97–24.65).

Adverse Events Associated with SSRIs and NSRIs The number of cases, reporting ratio, and the RORs of the SSRIs and NSRIs are summarized in Tables 7 and 8, respectively. Each table lists the 50 largest PTs in the reporting of the number of adverse events and sorts them by the value of the ROR. For the SSRI, suicidal events (completed suicide, suicide attempt, and suicidal ideation) were listed. The PTs of suicidal events (completed suicide and suicide attempt) were ranked high compared with those of anticholinergic side effects

Table 3. Adjusted ROR of SSRIs for Suicidal and Self-harm Events in Whole Data

	Likelihood ratio test	Adjusted ROR (95% CI)
Suicidal events[a)]		
SSRIs	<0.0001*	4.45 (4.35–4.56)
Male	<0.0001*	1.37 (1.35–1.40)
Reporting year	<0.0001*	0.99 (0.99–0.99)
Age (y.o.)		
<18	<0.0001*	1.20 (1.16–1.24)
18–24	<0.0001*	1.79 (1.73–1.84)
25–64 (as reference)		1
≥65	<0.0001*	0.23 (0.22–0.24)
Interaction term for SSRIs* age		
No SSRIs* 25–64 y.o. (as reference)		1
SSRIs* <18 y.o.	<0.0001*	9.58 (8.97–10.23)
SSRIs* 18–24 y.o.	0.1471	8.38 (7.89–8.90)
SSRIs* 25–64 y.o.	<0.0001*	4.45 (4.35–4.56)
SSRIs* ≥65 y.o.	<0.0001*	1.25 (1.18–1.33)
Self-harm events[b)]		
SSRIs	<0.0001*	5.27 (4.88–5.70)
Male	<0.0001*	1.19 (1.13–1.26)
Reporting year	0.0007*	1.02 (1.01–1.03)
Age (y.o.)		
<18	<0.0001*	3.70 (3.41–4.01)
18–24	<0.0001*	2.91 (2.64–3.20)
25–64 (as reference)		1
≥65	<0.0001*	0.17 (0.14–0.19)
Interaction term for SSRIs* age		
No SSRIs* 25–64 y.o. (as reference)		1
SSRIs* <18 y.o.	<0.0001*	31.40 (27.71–35.58)
SSRIs* 18–24 y.o.	0.0278*	18.69 (16.31–21.42)
SSRIs* 25–64 y.o.	<0.0001*	5.27 (4.88–5.70)
SSRIs* ≥65 y.o.	0.2457	1.04 (0.81–1.34)

a) It consisted of 4 PTs; "complete suicide," "suicidal ideation," "suicide attempt," and "suicidal behavior." *b*) It consisted of 3 PTs; "intentional self-injury," "self-injurious ideation," and "self-injurious behavior." *Statistically significant ($p<0.05$).

(pyrexia, agitation, confusional state, loss of consciousness, somnolence, and dizziness), which were defined using the MedDRA (Table 7). For NSRI, the PTs of suicidal events (suicide attempt and suicidal ideation) listed and ranked low compared with anticholinergic side effects (tachycardia, pyrexia, gait disturbance, loss of consciousness, confusional state, and agitation, Table 8).

DISCUSSION

The present study suggests that SSRIs might be associated with an increased risk of suicidal and self-harm events in patients aged under 18 using the FAERS database. The use of the logistic regression model, subset analysis, or both methods offers the possibility to control for covariates.

For suicidal and self-harm events, the adjusted RORs for the SSRIs in the <18 y.o. group had the highest values in the whole and subset data. The effects of the interaction terms for the SSRIs in the <18 y.o. patients were statistically significant in the whole and subset data (Tables 3, 4) and the estimated values for this term in the logistic regression exceeded 0 (whole data, the value of the interaction term for b5 in suicidal events was 0.58; subset data, the value of the interaction term for b5 in suicidal events was 0.39). Several studies have demonstrated differences in the risk of SSRI-related suicidality in patients of different ages; use of SSRIs may increase suicidality among children and adolescents,[2–5,8,9] whereas it may be associated with a decreased risk of suicidality in adults and the elderly.[9] In this study, we demonstrated a potentially increased risk of suicidality in patients administered SSRI <18 y.o.

The suicidal and self-harm events show a strong interdependent correlation,[29] and these two categories have been evaluated in previous reports. In a cohort study, the absolute risk of suicide was lower than that of attempted suicide or self-harm was with both SSRIs and TCAs.[30] Wijlaars *et al.*[5] reported that the incidence rate ratios of suicidal ideation were lower than those of self-harm with both SSRIs and TCAs were. In our results, the adjusted RORs of self-harm events were slightly higher than those of suicidal events were. Since the comparison of ROR is not recommended, our results have found that the tendency of the adjusted RORs was similar.

A previous study suggested that the age of a patient was one of the important confounding factors in the association between SSRI use and suicidality.[6] We observed a potential risk of suicidal events in the groups of children and adolescents (Table 4, adjusted ROR, 2.21 [95% CI, 1.85–2.62]), which could partly explain the high crude and adjusted RORs of suicidal events in patients aged 18 and younger administered SSRIs because the adjusted ROR for SSRIs in the <18 y.o. group was different from that in the 25–64 y.o. group in the present study.

Table 4. Adjusted ROR of SSRIs for Suicidal and Self-harm Events in Subset Data

	Likelihood ratio test	Adjusted ROR (95% CI)
Suicidal events[a]		
SSRIs	<0.0001*	1.42 (1.34–1.49)
Male	<0.0001*	1.50 (1.43–1.57)
Reporting year	<0.0001*	0.94 (0.93–0.95)
Age (y.o.)		
<18	<0.0001*	2.21 (1.85–2.62)
18–24	<0.0001*	1.89 (1.65–2.15)
25–64 (as reference)		1
≥65	<0.0001*	0.38 (0.33–0.42)
Interaction term for SSRIs* age		
No SSRIs* 25–64 y.o. (as reference)		1
SSRIs* <18 y.o.	<0.0001*	4.64 (4.15–5.19)
SSRIs* 18–24 y.o.	0.3821	2.47 (2.21–2.76)
SSRIs* 25–64 y.o.	<0.0001*	1.42 (1.34–1.49)
SSRIs* ≥65 y.o.	0.2030	0.48 (0.43–0.53)
Self-harm events[b]		
SSRIs	<0.0001*	1.71 (1.44–2.04)
Male	0.8510	1.01 (0.88–1.17)
Reporting year	0.0054*	0.97 (0.95–0.99)
Age (y.o.)		
<18	<0.0001*	4.16 (2.62–6.29)
18–24	<0.0001*	3.49 (2.44–4.85)
25–64 (as reference)		1
≥65	<0.0001*	0.31 (0.18–0.49)
Interaction term for SSRIs* age		
No SSRIs* 25–64 y.o. (as reference)		1
SSRIs* <18 y.o.	0.0003*	16.31 (13.12–20.29)
SSRIs* 18–24 y.o.	0.0807	8.50 (6.72–10.57)
SSRIs* 25–64 y.o.	<0.0001*	1.71 (1.44–2.04)
SSRIs* ≥65 y.o.	0.1706	0.33 (0.20–0.53)

a) It consisted of 4 PTs; "complete suicide," "suicidal ideation," "suicide attempt," and "suicidal behavior." *b*) It consisted of 3 PTs; "intentional self-injury," "self-injurious ideation," and "self-injurious behavior." *Statistically significant ($p<0.05$).

In this study, there was an association between treatment with SSRIs and suicidality in patients who were 25–64 y.o. (adjusted ROR for SSRIs in the 25–64 y.o. group in the subset analysis, 1.42 [95% CI, 1.34–1.49]), however, a systematic review demonstrated that exposure to SSRIs decreased the risk of suicidality in this age group.[9] In 2006, Baldessarini *et al.*[31] pointed out the instability in the suicidality risk difference between SSRIs and placebo. Several studies did not consider the severity of depression, which could contribute greatly to the instability of the suicidality risk difference among patients.[6] Depression severity is one of the important confounding factors, and this could not be corrected for in our analysis. It is possible that the patients receiving SSRIs were more severely depressed than those who were not. The prescription of SSRIs would indicate depression severity. In this scenario, the increased risk of suicide would be associated with depression severity rather than the SSRI prescription. The cases reported in the FAERS do not include detailed information about prescriptions. Therefore, we do not have a conclusive explanation for this data, and the suicidality risk of patients who are administered SSRIs should be studied further from the view point of the severity of the depression. Several aspects of patient backgrounds history, including fatal diseases or cancer may be confounding factors for depression and suicidal events. It might be considered that the patients with fatal diseases or cancer were more severely depressed than those without these conditions were. The information on patient background would be the indicator of depression severity. The FAERS database does not always contain enough patient background information to properly evaluate an event. These factors may have influenced the reporting strength of the events in clinical practice.

The intervention of regulatory authorities might influence the FAERS database reporting based on the year of reporting. In the present study, we did not analyze the FAERS data in the subsets as before/after the FDA regulation. In this study, we adjusted the ROR for the variable of the reporting year. Although the likelihood ratio test was significant ($p<0.0001$), the value of the adjusted ROR for reporting year was nearly one. We considered that the effects of reporting year were small. Further studies of these variables as covariates are necessary. Therefore, it might have been better if we had considered various clinical settings in our calculations.

Data subsetting is useful for evaluating drug-adverse event associations in the disproportionality analysis for SRSs because subsets consist of a population of patients that share a set of common risk factors and diseases.[16] The subsetting strategy mitigates the influence of confounding factors and bias.[17,18,32] Our results showed that values of the adjusted RORs in the subset analyses were lower than those in the whole data were. One potential explanation for the lower adjusted RORs is that the patients who were depressed subset

Table 5. Adjusted ROR of NSRIs for Suicidal and Self–harm Events in Whole Data

	Likelihood ratio test	Adjusted ROR (95% CI)
Suicidal events[a]		
NSRIs	<0.0001*	3.96 (3.79–4.14)
Male	<0.0001*	1.32 (1.30–1.35)
Reporting year	<0.0001*	0.98 (0.98–0.98)
Age (y.o.)		
<18	<0.0001*	1.28 (1.24–1.32)
18–24	<0.0001*	1.83 (1.78–1.89)
25–64 (as reference)		1
≥65	<0.0001*	0.23 (0.22–0.23)
Interaction term for NSRIs* age		
No NSRIs* 25–64 y.o. (as reference)		1
NSRIs* <18 y.o.	0.1358	4.27 (3.41–5.33)
NSRIs* 18–24 y.o.	0.0907	8.38 (7.17–9.81)
NSRIs* 25–64 y.o.	<0.0001*	3.96 (3.79–4.14)
NSRIs* ≥65 y.o.	0.0154*	1.06 (0.94–1.19)
Self-harm events[b]		
NSRIs	<0.0001*	2.55 (2.13–3.04)
Male	<0.0001*	1.14 (1.08–1.20)
Reporting year	0.8218	1.00 (0.99–1.01)
Age (y.o.)		
<18	<0.0001*	3.82 (3.56–4.09)
18–24	<0.0001*	3.07 (2.82–3.33)
25–64 (as reference)		1
≥65	<0.0001*	0.16 (0.14–0.18)
Interaction term for NSRIs* age		
No NSRIs* 25–64 y.o. (as reference)		1
NSRIs* <18 y.o.	0.9782	9.83 (5.99–16.13)
NSRIs* 18–24 y.o.	0.0023*	15.36 (10.73–21.99)
NSRIs* 25–64 y.o.	<0.0001*	2.55 (2.13–3.04)
NSRIs* ≥65 y.o.	0.4055	0.54 (0.30–0.97)

a) It consisted of 4 PTs; "complete suicide," "suicidal ideation," "suicide attempt," and "suicidal behavior." *b*) It consisted of 3 PTs; "intentional self-injury," "self-injurious ideation," and "self-injurious behavior." *Statistically significant ($p<0.05$).

had an intrinsic risk of suicidality, which may be a patient-related factor associated with adverse events. Our results of the subset analyses might reflect such an application of the data subsetting strategy, resulting in a decrease in the adjusted RORs compared with that in the analyses of the whole data. This result demonstrated the effects of confounding factors that can influence the analysis of the whole data.

In the subset data of suicidal events, the interaction term of the SSRIs in the ≥65 y.o. group was not statistically significant and the estimated value of the interaction term of SSRIs in the ≥65 y.o. group in the logistic regression fell below 0 (the value of the interaction term for b5 in suicidal events was −0.11, Table 4); however, this term was statistically significant in the whole data (Table 3). Previous studies reported that SSRIs did not increase the suicidality risk in patients aged ≥65 y.o.,[2,7,9] similar to the results of our subset analyses. Although we could not identify the cause of the difference between the whole and subset analysis, the effects of confounding factors such as an intrinsic risk of suicidality, co-administered drugs, and other unknown factors were present in the whole data. The results of the subset analyses were more acceptable than those of the analyses of the whole data were because the analyses were limited to a specific population of patients.

Since NSRIs such as TCAs, lack efficacy for depression treatment in young people and have a poor side-effect profile,[33] SSRIs are commonly prescribed for children and adolescents.[34] In our study, the effect of the interaction term for the NSRIs in the <18 y.o. group was statistically significant ($p=0.0010$) in suicidal events and, therefore, could not dispute that a relationship exists between NSRIs and suicidality in young people. Using the U.K. primary care database, Wijlaars *et al.*[5] reported that there were no systematic differences between the association of SSRIs and TCAs, and the incidence risk ratios for attempted suicide, suicidal ideation, or intentional self-harm in young people aged 10–18.

On the other hand, Coupland *et al.*[30] reported that suicidal or self-harm events were similar with SSRIs and TCAs in people aged 20–60. In our study, the effects of the term "NSRIs" for suicidal and self-harm events were not statistically significant in the subset data (Table 6). The PTs of suicidal events with SSRI were ranked high compared to those with NSRI (Tables 7, 8). It was difficult to evaluate the differences in the relative risk between SSRIs and NSRIs and, therefore, our result are not definitive. The benefits and risks of different antidepressant treatments will vary between patients.[35] In clinical practice, it is important to manage the anticholinergic side effects of TCAs while SSRIs induce significantly less anticholinergic and cardiotoxic adverse effects than TCAs do.[36] The use of SSRIs or NSRIs in children and adolescents should be adequately considered in terms of adverse events profile, between suicidal events and anticholinergic side effects, and

Table 6. Adjusted ROR of NSRIs for Suicidal and Self-harm Events in Subset Data

	Likelihood ratio test	Adjusted ROR (95% CI)
Suicidal events[a]		
NSRIs	0.3386	1.05 (0.95–1.17)
Male	<0.0001*	1.50 (1.43–1.58)
Reporting year	<0.0001*	0.94 (0.93–0.95)
Age (y.o.)		
<18	<0.0001*	2.99 (2.72–3.29)
18–24	<0.0001*	1.77 (1.63–1.93)
25–64 (as reference)		1
≥65	<0.0001*	0.36 (0.33–0.40)
Interaction term for NSRIs* age		
No NSRIs* 25–64 y.o. (as reference)		1
NSRIs* <18 y.o.	0.0010*	7.34 (4.60–11.72)
NSRIs* 18–24 y.o.	<0.0001*	4.45 (3.20–6.17)
NSRIs* 25–64 y.o.	0.3386	1.05 (0.95–1.17)
NSRIs* ≥65 y.o.	0.2544	0.32 (0.23–0.43)
Self-harm events[b]		
NSRIs	0.1404	1.29 (0.92–1.77)
Male	0.8546	1.01 (0.88–1.17)
Reporting year	0.0060*	0.97 (0.95–0.99)
Age (y.o.)		
<18	<0.0001*	8.92 (7.41–10.69)
18–24	<0.0001*	4.30 (3.54–5.20)
25–64 (as reference)		1
≥65	<0.0001*	0.25 (0.17–0.34)
Interaction term for NSRIs* age		
No NSRIs* 25–64 y.o. (as reference)		1
NSRIs* <18 y.o.	0.7573	9.90 (3.97–24.65)
NSRIs* 18–24 y.o.	0.0003*	17.45 (10.86–28.03)
NSRIs* 25–64 y.o.	0.1404	1.29 (0.92–1.77)
NSRIs* ≥65 y.o.	0.5182	0.20 (0.05–0.81)

a) It consisted of 4 PTs; "complete suicide," "suicidal ideation," "suicide attempt," and "suicidal behavior." *b*) It consisted of 3 PTs; "intentional self-injury," "self-injurious ideation," and "self-injurious behavior." *Statistically significant ($p<0.05$).

in terms of benefit-risk balance.

The data subsetting strategy does not control for "channeling bias," which is the potential for drugs to be prescribed differently based on the disease severity.[32] The effect of this parameter was not adjusted for in the calculation of the ROR by applying logistic regression analysis because we could not obtain data on the severity and duration of the disease from the FAERS database. Our results should be regarded as containing some biases; in addition to the "channeling bias," other sources of bias are inherently and unavoidably included in the SRS data.

The FAERS database is subject to over-reporting, under-re-

Table 7. Adverse Events Associated with SSRIs in Subset Data

Preferred terms	PT code	Total	Cases	ROR (95% CI)	RR (%)
Total		97501	46767		48.0
Completed suicide	10010144	1772	1147	2.02 (1.83–2.22)	64.7
Serotonin syndrome	10040108	1663	1069	1.97 (1.78–2.18)	64.3
Hyponatraemia	10021036	1505	925	1.74 (1.57–1.94)	61.5
Type 2 diabetes mellitus	10067585	1999	1210	1.68 (1.54–1.84)	60.5
Aggression	10001488	1812	1089	1.65 (1.50–1.81)	60.1
Suicide attempt	10042464	2562	1494	1.53 (1.42–1.66)	58.3
Abdominal pain	10000081	1701	980	1.48 (1.35–1.64)	57.6
Overdose	10033295	1591	910	1.46 (1.32–1.61)	57.2
Drug interaction	10013710	3830	2173	1.44 (1.35–1.54)	56.7
Chest pain	10008479	1926	1075	1.38 (1.26–1.51)	55.8
Back pain	10003988	1424	792	1.37 (1.23–1.52)	55.6
Pyrexia	10037660	1938	1070	1.35 (1.23–1.47)	55.2
Suicidal ideation	10042458	4478	2450	1.33 (1.25–1.41)	54.7
Pain in extremity	10033425	1733	943	1.30 (1.18–1.43)	54.4
Pain	10033371	3716	1993	1.27 (1.19–1.35)	53.6
Blood cholesterol increased	10005425	1460	783	1.26 (1.14–1.40)	53.6
Diabetes mellitus	10012601	2758	1458	1.22 (1.13–1.32)	52.9
Arthralgia	10003239	2015	1063	1.22 (1.11–1.33)	52.8
Fall	10016173	3296	1736	1.22 (1.13–1.30)	52.7
Tremor	10044565	3823	2002	1.20 (1.13–1.28)	52.4
Anxiety	10002855	6609	3436	1.19 (1.13–1.25)	52.0
Agitation	10001497	2803	1456	1.18 (1.09–1.27)	51.9
Dyspnoea	10013968	3005	1557	1.17 (1.09–1.26)	51.8
Confusional state	10010305	2994	1548	1.17 (1.08–1.26)	51.7
Depression	10012378	8362	4257	1.14 (1.09–1.19)	50.9
Vomiting	10047700	3656	1857	1.12 (1.05–1.20)	50.8
Asthenia	10003549	2809	1415	1.10 (1.02–1.19)	50.4
Diarrhoea	10012735	3567	1786	1.09 (1.02–1.17)	50.1
Fatigue	10016256	4917	2446	1.08 (1.02–1.14)	49.7
Decreased appetite	10061428	1656	824	1.08 (0.98–1.19)	49.8
Weight decreased	10047895	2243	1113	1.07 (0.98–1.16)	49.6
Loss of consciousness	10024855	1968	975	1.07 (0.98–1.17)	49.5
Hypertension	10020772	2196	1083	1.06 (0.97–1.15)	49.3
Convulsion	10010904	2557	1254	1.05 (0.97–1.13)	49.0
Weight increased	10047899	3203	1549	1.02 (0.95–1.09)	48.4
Malaise	10025482	3259	1575	1.02 (0.95–1.09)	48.3
Irritability	10022998	1943	923	0.98 (0.90–1.07)	47.5
Somnolence	10041349	3057	1436	0.96 (0.89–1.03)	47.0
Drug ineffective	10013709	6638	3110	0.95 (0.91–1.00)	46.9
Pruritus	10037087	1636	763	0.95 (0.86–1.04)	46.6
Hyperhidrosis	10020642	2632	1227	0.95 (0.88–1.02)	46.6
Dizziness	10013573	6075	2790	0.92 (0.87–0.97)	45.9
Rash	10037844	1851	847	0.91 (0.83–1.00)	45.8
Paraesthesia	10033775	2416	1077	0.87 (0.80–0.94)	44.6
Condition aggravated	10010264	2275	1010	0.86 (0.79–0.94)	44.4
Nausea	10028813	7327	3234	0.85 (0.81–0.89)	44.1
Headache	10019211	5884	2590	0.84 (0.80–0.89)	44.0
Feeling abnormal	10016322	3905	1667	0.80 (0.75–0.85)	42.7
Insomnia	10022437	5805	2477	0.80 (0.76–0.84)	42.7
Drug withdrawal syndrome	10013754	3255	1287	0.70 (0.65–0.75)	39.5

porting, missing data, exclusion of healthy individuals, lack of a denominator, and the presence of confounding factors.[32,37] Furthermore, the cases reported in the FAERS database do not always contain sufficient information to allow for proper evaluation. Because of these common deficits within the SRS, disproportionality measures (ROR) do not allow risk quantification but only offer a rough indication of the strength of the signal and, thus, are only relevant to the *hypothesis*.[25] The ROR indicates an increased risk of adverse event reporting and does not indicate the risk of adverse event occurrence in absolute terms.[38] Therefore, special and careful attention has to be paid to the interpretation of results obtained by analyz-

Table 8. Adverse Events Associated with NSRIs in Subset Data

Preferred terms	PT code	Total	Cases	ROR (95% CI)	RR (%)
Total		97501	5786		5.9
Type 2 diabetes mellitus	10067585	1999	262	2.46 (2.15–2.81)	13.1
Tachycardia	10043071	999	123	2.25 (1.86–2.73)	12.3
Pyrexia	10037660	1938	236	2.25 (1.96–2.58)	12.2
Syncope	10042772	1215	145	2.18 (1.83–2.60)	11.9
Serotonin syndrome	10040108	1663	190	2.08 (1.78–2.43)	11.4
Anaemia	10002034	1102	121	1.98 (1.63–2.39)	11.0
Diabetes mellitus	10012601	2758	294	1.94 (1.71–2.19)	10.7
Overdose	10033295	1591	162	1.82 (1.54–2.15)	10.2
Blood cholesterol increased	10005425	1460	143	1.74 (1.46–2.07)	9.8
Pneumonia	10035664	1234	121	1.74 (1.44–2.10)	9.8
Pain in extremity	10033425	1733	166	1.70 (1.44–2.00)	9.6
Gait disturbance	10017577	1450	138	1.68 (1.41–2.01)	9.5
Oedema peripheral	10030124	1376	130	1.67 (1.39–2.00)	9.4
Fall	10016173	3296	305	1.65 (1.46–1.86)	9.3
Drug interaction	10013710	3830	349	1.63 (1.45–1.82)	9.1
Back pain	10003988	1424	130	1.61 (1.34–1.93)	9.1
Abdominal pain	10000081	1701	155	1.61 (1.36–1.90)	9.1
Loss of consciousness	10024855	1968	179	1.60 (1.37–1.88)	9.1
Constipation	10010774	1518	133	1.53 (1.28–1.84)	8.8
Chest pain	10008479	1926	167	1.52 (1.29–1.79)	8.7
Hypertension	10020772	2196	183	1.46 (1.25–1.70)	8.3
Dyspnoea	10013968	3005	242	1.41 (1.23–1.61)	8.1
Confusional state	10010305	2994	241	1.40 (1.23–1.61)	8.0
Arthralgia	10003239	2015	160	1.38 (1.17–1.62)	7.9
Pain	10033371	3716	283	1.32 (1.17–1.50)	7.6
Asthenia	10003549	2809	209	1.28 (1.11–1.48)	7.4
Tremor	10044565	3823	281	1.27 (1.12–1.44)	7.4
Agitation	10001497	2803	205	1.26 (1.09–1.46)	7.3
Suicide attempt	10042464	2562	186	1.25 (1.07–1.45)	7.3
Pruritus	10037087	1636	119	1.25 (1.03–1.51)	7.3
Convulsion	10010904	2557	180	1.21 (1.03–1.41)	7.0
Hyperhidrosis	10020642	2632	184	1.20 (1.03–1.39)	7.0
Malaise	10025482	3259	225	1.18 (1.03–1.36)	6.9
Somnolence	10041349	3057	210	1.18 (1.02–1.36)	6.9
Depression	10012378	8362	556	1.14 (1.04–1.25)	6.6
Weight decreased	10047895	2243	148	1.12 (0.95–1.33)	6.6
Diarrhoea	10012735	3567	233	1.11 (0.97–1.27)	6.5
Weight increased	10047899	3203	209	1.11 (0.96–1.28)	6.5
Vomiting	10047700	3656	235	1.09 (0.95–1.25)	6.4
Anxiety	10002855	6609	408	1.05 (0.94–1.16)	6.2
Headache	10019211	5884	346	0.99 (0.88–1.11)	5.9
Suicidal ideation	10042458	4478	260	0.98 (0.86–1.11)	5.8
Fatigue	10016256	4917	283	0.97 (0.85–1.09)	5.8
Condition aggravated	10010264	2275	125	0.92 (0.77–1.10)	5.5
Dizziness	10013573	6075	325	0.89 (0.79–1.00)	5.3
Insomnia	10022437	5805	304	0.87 (0.77–0.98)	5.2
Nausea	10028813	7327	362	0.81 (0.73–0.91)	4.9
Drug ineffective	10013709	6638	314	0.77 (0.69–0.87)	4.7
Feeling abnormal	10016322	3905	157	0.65 (0.56–0.77)	4.0
Drug withdrawal syndrome	10013754	3255	124	0.62 (0.52–0.74)	3.8

ing data from the FAERS database.

Recently, several researchers demonstrated that disproportionality measures can provide new—and even causal—insights. These studies each used an approach that might circumvent biases such as selection and reporting biases because this approach mitigates the effect of confounding factors, thereby enhancing the robustness of the result. However, reports on safety signal detection with logistic regression analyses focusing on age stratification are scarce.

To the best of our knowledge, this is the first study to investigate the influence of SSRI treatment on suicidality in terms of age-stratified patient groups using logistic regression and subset analyses. Despite the limitations inherent to SRSs, we obtained reasonable results in the context of those reported in the literature.[2–9] We consider the results of the FAERS database analysis to be valid owing to the appropriate analysis method and the special attention paid to potential bias, and believe that the logistic regression and subset analyses are valuable in the disproportionality analysis.

We demonstrated that the effect of age on the association between SSRI-related suicidal and self-harm events could not be ignored. Our results show that children and adolescents should be closely monitored for the occurrence of suicidality when they are prescribed SSRIs. Further epidemiological studies such as case-control or cohort studies are necessary to determine more precisely the effect of patient age on SSRI-related suicidality.

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