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Longitudinal bidirectional relationships between maternal depressive/anxious symptoms and children's tic frequency in early adolescence

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24 **Keywords: tics, tic frequency, maternal depressive/anxious symptoms, longitudinal study,**
25 **general population study, early adolescence.**

26 **Abstract**

27 Background: Previous studies have revealed an association between maternal depressive/anxious
28 symptoms and children's tics. However, the longitudinal relationships between these symptoms
29 remain unclear. We examined the longitudinal relationships between maternal depressive/anxious
30 symptoms and children's tic frequency in early adolescence with a population-based sample.

31 Methods: The participants consisted of 3,171 children and their mothers from the Tokyo Teen Cohort
32 (TTC) study, a population-representative longitudinal study that was launched in Tokyo in 2012.
33 Maternal depressive/anxious symptoms and children's tics were examined using self-report
34 questionnaires at the ages of 10 (time 1, T1) and 12 (time 2, T2). A cross-lagged model was used to
35 explore the relationships between maternal depressive/anxious symptoms and children's tic
36 frequency.

37 Results: Higher levels of maternal depressive/anxious symptoms at T1 were related to an increased
38 children's tic frequency at T2 ($\beta = .06, p < .001$). Furthermore, more frequent children's tics at T1
39 were positively related to maternal depressive/anxious symptoms at T2 ($\beta = .06, p < .001$).

40 Conclusions: These findings suggest a longitudinal bidirectional relationship between maternal
41 depressive/anxious symptoms and children's tic frequency in early adolescence that may exacerbate
42 each other over time and possibly create a vicious cycle. When an early adolescent has tics, it might
43 be important to identify and treat related maternal depressive/anxious symptoms.

44

45 **Introduction**

46 Tics are sudden, rapid, recurrent, and nonrhythmic motor movements or vocalizations. The Diagnostic
47 and Statistical Manual of Mental Disorders, 5th edition (DSM-5) includes three tic disorders (1).
48 Tourette syndrome (TS) is defined by the presence of at least two motor tic behaviors and one vocal
49 tic behavior for a minimum period of a year, manifesting before the age of 18. Chronic tic disorder
50 (CT) is defined by the presence of either motor or vocal tics for at least 1 year, while provisional tic
51 disorder is defined as tics that have been present for less than a year. Recent population-based studies
52 have demonstrated that tics are more common than previously recognized (2-5). According to the
53 International Classification of Diseases 10th Revision (ICD-10), which is an international diagnostic
54 classification developed by the World Health Organization (WHO), one in five to ten children has
55 experienced tics (6). Tic disorders impose a psychosocial burden on children and their families because
56 tics are characterized by the visibility of symptoms, which can cause stigma and prejudice (7-10).
57 Attention-deficit/hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD) are
58 common comorbidities of tic disorders (7, 11, 12). Tic disorders tend to be remitted with age through
59 adolescence (7, 13, 14). The overall similarity in these patterns of comorbidity and natural history
60 among tic disorders suggests that tic disorders have etiological continuity (15-17), and a recent
61 diagnosis of "tic spectrum disorders" has been suggested (18). Many clinical studies and experimental
62 studies historically use tic frequency on measures to assess severity at outcome (19-24).

63 Tic disorders consist of a complex involvement of both multiple genes and environmental
64 factors (25, 26). Little is known about the exact brain mechanisms associated with tic development and
65 expression (27, 28), although preliminary evidence from neurochemical and neuroimaging
66 investigations suggests a primary role for dysfunction of the dopaminergic pathways within the cortico-
67 striato-cortico-frontal circuitry (29-31). Environmental factors for tics include infection and
68 autoimmune dysfunction, maternal environment during pregnancy, and psychosocial stress (11, 28). It
69 has been suggested that psychosocial factors such as trauma and intense daily psychological stress may
70 be risk factors in individuals with genetic vulnerabilities to TS (11, 32).

71 The identification of parental psychopathology could be informative in the evaluation of risk
72 factors for the development of tic disorders in children (33). Previous research has shown that there is
73 an association between maternal psychiatric symptoms and children's tic disorders. Chronic maternal

74 anxious symptoms and prenatal maternal depressive symptoms have been associated with increased
75 odds of children having TS/CT at age 13 (34). In another study, a maternal history of nonspecific
76 psychiatric disorders, including anxiety disorders and depressive disorders, was shown to increase odds
77 of children having TS/CT during childhood and adolescence (35). It is presumed that maternal
78 depressive/anxious symptoms are associated with the occurrence of children's TS/CT via maternal-
79 specific environmental and/or genetic factors (34, 35).

80 Although the association between maternal mental health and children's tic disorders has
81 been proved (34, 35), it is not clear whether maternal psychiatric symptoms are associated with the
82 subsequent course of children's tic disorders. If maternal psychiatric symptoms predict the subsequent
83 course of children's tic disorders, then maternal psychiatric symptoms could possibly be a prognostic
84 factor or an intervention target of tic disorders. To examine this point, we investigated the relationship
85 between maternal depressive/anxious symptoms and children's tic frequency in early adolescence with
86 a longitudinal design.

87 In addition, we speculated that maternal depressive/anxious symptoms and children's tic
88 frequency influence each other bidirectionally. Some studies have shown bidirectional influences on
89 maternal and children's psychiatric symptoms. For example, depression in mothers increases the risk
90 of emotional and behavioral problems in their children and vice versa (36, 37). However, no study has
91 investigated the bidirectional relationship between maternal psychiatric symptoms and children's tics.
92 Research on the longitudinal bidirectional relationship between maternal depressive/anxious symptoms
93 and children's tics would be helpful in advancing the research and practices related to tics.

94 Our aim was therefore to examine the relationships between maternal depressive/anxious
95 symptoms and child's tic frequency in a longitudinal study design using a general population of early
96 adolescent samples. In this population-based study, we referred to a tic or tics instead of the diagnostic
97 term "tic disorders" because we did not make clinical diagnoses of the participants. Our hypotheses
98 were as follows: 1) maternal depressive/anxious symptoms predict children's tic frequency two years
99 later, and 2) maternal depressive/anxious symptoms and children's tic frequency influence each other
100 bidirectionally over time.

101

102 **Materials and Methods**

103 **Participants**

104 This study used data from the Tokyo Teen Cohort (TTC) study (<http://ttcp.umin.jp/>), a population-
105 based longitudinal survey focusing on children's health from biopsychosocial multidisciplinary
106 viewpoints (38). The TTC study has started from October 2012 and is currently being conducted. The
107 participants were recruited from three municipalities in Tokyo (Setagaya, Mitaka, and Chofu) using
108 the Basic Resident Register. The candidate participants were 14,553 children born between September
109 1, 2002, and August 31, 2004 (Figure 1). Invitation letters were sent to the primary parents of those
110 children around their tenth birthday. Of these children, 10,234 were successfully contacted, and these
111 children were invited to participate in the cohort study. Of these 10,234 children, 4,478 children
112 participated in the baseline survey named the Tokyo Early Adolescence Survey (T-EAS). This baseline
113 survey was conducted from October 2012 to January 2015, when the participants were approximately
114 10 years old (time 1, T1). Among the 4,478 participants in the T-EAS, candidates were chosen as
115 participants for the second wave of the TTC study. For the sake of cohort management, the target
116 number of participants to be included in the second wave of the TTC was 3,000 children. When

117 choosing these TTC participants, an oversampling method was used instead of inclusion criteria,
118 considering the low follow-up rate of families with low annual household incomes. Among children
119 who participated in T-EAS and were interested in participating in the cohort study, all 620 children
120 whose household annual income was lower than 4,990 thousand yen were invited. From the remaining
121 3,858 children, 2,551 children were randomly invited to the second wave of TTC. Thus, 3,171
122 participants were extracted as targets for the second wave of the TTC study. The second wave of the
123 TTC study was carried out from August 2014 to December 2016, at the time when the participants
124 were approximately 12 years old (time 2, T2). Of the 3,171 children who were invited, 3,007
125 individuals participated in the second wave of the TTC study (follow-up rate 94.8%). In each wave of
126 the data collection, trained interviewers visited the participants' homes. They distributed questionnaires
127 to the children and primary parents (mostly mothers), and they conducted psychological tests on the
128 children.

129

130 **Ethical approval**

131 Ethical approval for this study was obtained from the research ethics committees of the Tokyo
132 Metropolitan Institute of Medical Science (Approval number: 12-35), The Graduate University for
133 Advanced Studies, SOKENDAI (2012002), and the Graduate School of Medicine and Faculty of
134 Medicine, The University of Tokyo (10057). We obtained informed assent from the children and
135 written informed consent from their primary parents.

136

137 **Measures**

138 *Tic frequency*

139 We evaluated tic frequency at T1 and T2. The participants' primary parents answered a questionnaire
140 about the children's tics; this questionnaire has been used in a previous study (5). The questionnaire
141 includes a section with the following five questions about specific motor and vocal tics in the past year:
142 "Q1: Has your child had any repeated movements of parts of the face and head (e.g., eye blinking,
143 grimacing, sticking tongue out, licking lips, spitting)?" "Q2: Has your child had repeated movements
144 of the neck, shoulder or trunk (e.g., twisting around, shoulder shrugging, bending over, nodding)?"
145 "Q3: Has your child had repeated movements of the arms, hands, legs, or feet?" "Q4: Has your child
146 had repeated noises and sounds (e.g., coughing, clearing throat, grunting, gurgling, hissing)?" and
147 "Q5: "Has your child had repeated words or phrases?" Each question is answered as either "definitely",
148 "probably" or "not at all" present. Furthermore, we asked the following question about the frequency
149 of these repetitive behaviors: "Q6: About how often does/did this happen in the last year?" This
150 question was answered on the following 5-point Likert scale: "1: less than once a month, 2: 1-3 times
151 a month, 3: about once a week, 4: more than once a week, 5: every day." We defined the participants
152 who responded "definitely" or "probably" to any of Q1, Q2, and Q4 as having tics. The participants
153 who only endorsed repeated movements of the arms, hands, legs or feet (Q3) or repeated words or
154 phrases (Q5) in the absence of a positive response to the other questions about the types of tics (Q1,
155 Q2, Q4) were excluded from a case definition to remove nontic movements such as stereotypy or
156 isolated echolalia. We defined as tics all responses of "definitely" or "probably" to questions
157 concerning motor and/or vocal tics regardless of their frequency because there is no condition of
158 frequency in the diagnostic criteria of tic disorders (1) and because we aimed to exhaustively find tics
159 in the general population. For those without tics, the frequency of tics was regarded as 0, and for those

160 with tics, the frequency of tics was evaluated on a 5-point scale from the answer in Q6.

161

162 *Maternal depressive/anxious symptoms*

163 We employed the Kessler Psychological Distress Scale (K6) (39-41) for T1 and the General Health
164 Questionnaire-28 (GHQ-28) (42, 43) for T2. The K6 and the GHQ-28 are both widely used self-report
165 questionnaires that were developed to evaluate depressive/anxious symptoms. We used different scales
166 between T1 and T2 in the current study because the TTC study also switched the scale used for maternal
167 depressive/anxious symptoms from the K6 to the GHQ-28 starting at T2. The K6 is a short
168 questionnaire consisting of 6 questions about the subjective mental distress of the respondent over the
169 past 30 days that are answered on a 5-point scale, and the scores of the 6 items are added together (0-
170 24 points). The GHQ-28 consists of 28 questions about the respondent's subjective physical and mental
171 states over the past few weeks, with a total score being calculated for each item by giving 0 points each
172 for the right two responses and 1 point each for the left two responses (0-28 points). Cutoff values are
173 often used to screen for anxiety disorders and depression when assessing the K6 and the GHQ-28.
174 However, in this study, we used raw values of the K6 and the GHQ-28 as continuous scales instead of
175 screening scales, for the purpose of evaluating the severity of depressive/anxious symptoms, including
176 the normal range in the general population. The Cronbach's alpha value was .84 for the K6 and .88 for
177 the GHQ-28. We found that the distributions of the K6 and the GHQ-28 were similar based on the
178 graphing cumulative distribution of their Z scores (Supplementary Figure 1). If a primary parent other
179 than a mother answered the K6 or the GHQ-28, we regarded those responses as missing values.

180

181 *Other variables*

182 Sex (5, 7, 44), age (32, 45, 46), maternal age (35, 47-49), socioeconomic status (50), and maternal
183 alcohol use during pregnancy (51) were included in the analyses since previous studies have reported
184 that these factors influence the occurrence of TS/CT. The data for these variables were obtained from
185 the responses to the questionnaires completed by caregivers. To assess socioeconomic status, family
186 income was evaluated on an 11-point scale, which ranged from "0-990,000 yen" to "more than
187 10,000,000 yen." Information on maternal alcohol use during pregnancy was obtained from maternity
188 record books that were provided for almost all mothers by local public organizations in Japan.

189

190 **Statistical analysis**

191 Longitudinal relationships between maternal depressive/anxious symptoms and children's tic
192 frequency were studied with structural equation modeling. We used SPSS® (Statistical Package for
193 Social Science; IBM Corp., Armonk, N.Y. USA) version 21.0 for the characteristics of the study
194 participants and Amos ver. 22.0 (IBM Corp, New York) for the structural equation modeling. We used
195 the following two cross-lagged design models. The first model analyzed the longitudinal relationships
196 between maternal depressive/anxious symptoms and children's tic frequency without adjusting for
197 covariates (unadjusted model). The second model adjusted for sex, age in months, family income,
198 maternal age, and maternal alcohol use during pregnancy (adjusted model).

199 Missing values in the categories of tics, maternal depressive/anxious symptoms, and the

200 covariates were accounted for by full information maximum likelihood procedures available in Amos.
201 This method estimates model parameters and standard errors using all available data while adjusting
202 for the uncertainty associated with missing data (52).

203 The threshold for statistical significance was set to $p < .05$ (two-sided) for all analyses. We
204 evaluated the fit of our models by using the comparative fit index (CFI) and the root mean square error
205 of approximation (RMSEA). A good model fit was indicated by an RMSEA value smaller than .05 and
206 a CFI value larger than .95 (53, 54).

207

208 **Results**

209 **Characteristics of the study participants**

210 Table 1 shows the demographic characteristics of the 3,171 study participants. Of the 3,171 included
211 children, 2,601 children (82.0%) had complete data about tics across both time points; 67 (2.1%) and
212 484 (15.3%) children had missing data about tics in either T1 or T2, respectively, and 19 (0.6%)
213 children had missing data about tics in both T1 and T2. Across both time points, data about maternal
214 depressive/anxious symptoms were complete for 2,683 mothers (84.6%); 24 (0.8%) and 309 (9.7%)
215 mothers had missing scores in either T1 or T2, respectively; and 155 mothers (4.9%) had missing data
216 about maternal depressive/anxious symptoms in both T1 and T2.

217 Of the participants, 23.3% children (720 of 3,085 available data) at T1 and 23.5% children
218 (626 of 2,668 available data) at T2 had tics. These prevalence rates are consistent with previous studies
219 that have estimated the point prevalence of tics in childhood to be approximately 20-29% (2-4). Of the
220 2,601 people whose data on the presence of tics were obtained in both T1 and T2, 332 participants
221 endorsed tics at both T1 and T2, 280 participants endorsed tics only for T1, 265 participants endorsed
222 tics for only T2, and 1,724 did not endorse tics at either time point.

223

224 **Longitudinal relationships between maternal depressive/anxious symptoms and children's tic**
225 **frequency in early adolescence**

226 We investigated the relationships between maternal depressive/anxious symptoms and children's tic
227 frequency in a cross-lagged model analysis (Figure 2, Table 2). There was a cross-sectional association
228 between maternal depressive/anxious symptoms and child's tic frequency at T1 and T2. Higher levels
229 of maternal depressive/anxious symptoms at T1 significantly increased children's tic frequency at T2
230 (adjusted model: $\beta = .06, p < .001$). In contrast, higher frequency of children's tics at T1 was related
231 to higher levels of maternal depressive/anxious symptoms at T2 (adjusted model: $\beta = .06, p < .001$).
232 All of these models indicated good model fit to the data (adjusted model: CFI = .950, RMSEA = .046).
233 These results revealed that maternal depressive/anxious symptoms and children's tic frequency had
234 longitudinal, bidirectional relationships with each other.

235

236 **Discussion**

237 This was the first study to examine the longitudinal relationships between maternal depressive/anxious

238 symptoms and children's tic frequency in a population-based early adolescent sample. The following
239 two findings were obtained. First, when more severe maternal depressive/anxious symptoms are
240 present, children are likely to present more frequent tics two years later. Second, the severity of
241 maternal depressive/anxious symptoms and children's tic frequency are longitudinally associated with
242 each other.

243 The present results showed cross-sectional relationship between maternal anxiety/depressive
244 symptoms and children's tic frequency and small but significant longitudinal bidirectional relationship
245 between them. Previous studies showed relationship between past maternal mental symptoms and
246 children's TS/CT, and presumed that maternal mental symptoms are associated with the occurrence of
247 children's TS/CT via maternal-specific environmental and/or genetic factors (34, 35). The present
248 results is consistent with those previous studies and provided a new perspective that suggests
249 longitudinal bidirectional relationship between maternal anxiety/depressive symptoms and children's
250 tic frequency.

251 Several explanations may be possible for the significant magnitude-response relationship
252 between maternal depressive/anxious symptoms and children's later tic frequency. First, maternal
253 depressive/anxious symptoms may affect the occurrence, persistence, and exacerbation of children's
254 tics as an environmental factor because environmental factors such as psychosocial stresses are known
255 to exacerbate tics (55-59). In addition, several studies have shown that tic frequency can be influenced
256 by antecedent environmental events and social consequences although they referred relatively
257 immediate and short term reaction. For example, some activities reduce tic frequency such as focusing
258 attention away from tics (60), aerobic exercise training (61) and participation in musical activity
259 (62). There are no reports of an association between maternal psychiatric symptoms and the course of
260 children's tics. However, some studies have shown an association between maternal psychiatric
261 symptoms and the course of children's psychiatric symptoms. For example, maternal depression has
262 been shown to be associated with increased psychiatric diagnoses and emotional and behavioral
263 problems in children, and when maternal depression is remitted, the children's problems are more
264 likely to also be in remission (63). Furthermore, improvement in parental depression has a positive
265 impact on the health, emotional, cognitive, academic and overall functioning of children (64). Thus,
266 similar to these reports, maternal depressive/anxious symptoms might affect the course of children's
267 tics as an environmental factor. Second, there might be genetic relationships between maternal
268 depressive/anxious symptoms and the occurrence, persistence, and exacerbation of tics. Family studies
269 of TS have suggested that TS has genetic correlations with depressive disorders and anxiety disorders
270 (65, 66), although these correlations are possibly mediated through ADHD and OCD (66). There has
271 been no research examining the genetic relationships between maternal depressive/anxious symptoms
272 and the persistence or exacerbation of tics, but the results of this research could not rule out these
273 possibilities. Furthermore, there is also a possibility that an interaction of genetic and environmental
274 factors is involved in the relationships between maternal depressive/anxious symptoms and children's
275 tics. The results of this study could not distinguish genetic and environmental contributors to the
276 relationships between maternal depressive/anxious symptoms and children's tics.

277 Our findings on the association between children's tic frequency and increased maternal
278 depressive/anxious symptoms two years later can be explained by several potential mechanisms. One
279 of the possible mechanisms is that the parenting stress associated with bringing up children with tics
280 might influence maternal depressive/anxious symptoms. Parents of children with TS experience
281 increased levels of caregiver burdens and parenting stress compared to parents of children without TS
282 (67, 68). The visible nature of tics can have an impact on the parent-child relationship, with parents
283 becoming overprotective of, worrying about, struggling to accept or trying to control children's tics,

284 which can lead to family conflicts, poor parent-child relationships and increased frustrations in
285 parenting (7, 9, 10, 69, 70). Parenting stress in parents of children with tics could also occur due to
286 children's comorbidities, such as ADHD, OCD, and behavioral problems (67, 68). In a previous
287 population-based study, 21.2% of children had tics, and children with tics were more affected by
288 psychopathologies, including ADHD and OCD, than were children without tics (12). In addition to
289 these environmental factors, both genetic factors and genetic/environmental interactions might have an
290 effect of children's tics on maternal depressive/anxious symptoms.

291 The implications of this study were that the longitudinal bidirectional relationships between
292 maternal depressive/anxious symptoms and children's tic frequency may suggest a vicious cycle in
293 which maternal depressive/anxious symptoms make tic frequency increased, and children's tic
294 frequency make maternal depressive/anxious symptoms worse. This study also suggested that not only
295 intervention in children's tics but also intervention in maternal depressive/anxious symptoms might be
296 important for the treatment of tics. However, the present study was unable to separate genetic and
297 environmental factors in the association between children's tic frequency and maternal
298 depressive/anxious symptoms; therefore, further research is needed to determine the effect of
299 intervention on maternal anxiety/depressive symptoms. While there has been a consensus on the
300 importance of family psychoeducation in the treatment of tics (7, 27), it is not known whether maternal
301 psychiatric problems influence the course of children's tics. This study provides new insights for future
302 research and practice.

303 The strength of this study was that, for the first time, it was shown that higher levels of
304 maternal depressive/anxious symptoms are related to an increased children's tic frequency two years
305 later and that there are longitudinal relationships between maternal depressive/anxious symptoms and
306 children's tic frequency. Other strengths were the large sample size, the high follow-up rate of the
307 study, and the inclusion of nonclinical tics. In contrast, this study also had several limitations. First, we
308 used different measures of maternal depressive/anxious symptoms for T1 and T2. We found that the
309 distributions of the K6 and the GHQ-28 were similar by graphing the cumulative distribution of the Z
310 scores of the K6 and the GHQ-28 (Supplementary Figure 1). Additionally, this limitation did not
311 influence the course from maternal depressive/anxious symptoms to children's tic frequency. Second,
312 in this study, children's tics were evaluated not by direct clinical assessments but by questionnaires to
313 caregivers. However, we deliberately chose rigorous tic definitions and sought to exclude participants
314 with nontic movement disorders (e.g., stereotypies associated with autism or an intellectual disability,
315 repetitive arm/leg movements that could be better explained by tremor or motor restlessness) (5). In
316 this study, the prevalence of tics was 23.3% at age 10 and 23.5% at age 12. These prevalence rates
317 could be considered reasonable based on the following evidence. Point prevalence depends strongly
318 on age; the highest rate is estimated to be approximately 20% at age 5-10, and the lifetime prevalence
319 is much higher (3). In previous studies that have directly observed children, tics were found in 29.2%
320 of fourth-grade children in an elementary school in Washington D.C. (2) and in 21.2% of children aged
321 9-17 years old (mean 13.1 years old) in Monroe County, Rochester, New York (4). The prevalence
322 rates of tics in the present study were consistent with those found in these previous studies. Third, the
323 data analysis in this study could not adjust for ADHD and OCD, which are frequently comorbid with
324 tics. That may be because of the strong association of tics with ADHD and OCD. Future studies are
325 needed to examine the effects of ADHD and OCD on the bidirectional relationships between maternal
326 depressive/anxious symptoms and children's tic frequency. The fourth limitation was that the research
327 interval in this longitudinal study was relatively short. Typically, tics improve gradually during
328 adolescence, with repeated periods of remission and exacerbation. Thus, it might be difficult to capture
329 change in the short research period of two years. Longer-term follow-up periods are needed in the
330 future. The fifth limitation was that we did not collect information about the maternal history of tics.

331 Given the low rate of medical consultation for tics (5, 12, 65) and the clinical outcome that tics often
332 improve or disappear after adolescence (7, 13, 14), it is probably not possible to obtain accurate
333 information on the maternal history of tics. Finally, there were also some limitations inherent to the
334 cross-lagged model (71); i.e., there is a possibility that there are multiple potential additional factors
335 (not included in the model) that influence the bidirectional relationship over time.

336 The following two studies would be helpful in testing the viability of the relationships
337 between maternal depressive/anxious symptoms and children's tic frequency and in advancing research
338 and practice. First, if the course of children's tic frequency could be observed at three or more time
339 points, it would be possible to confirm the vicious cycle that develops between maternal
340 depressive/anxious symptoms and children's tics and to investigate the mediating factors. For example,
341 children's anxiety/depression symptoms might mediate the relationships between maternal
342 depressive/anxious symptoms and children's tic frequency. In addition, comorbidities or poor quality
343 of life might mediate the relationships between children's tic frequency and maternal
344 depressive/anxious symptoms. Second, intervention studies could examine whether improvements in
345 maternal depressive/anxious symptoms improve children's tics.

346 This study was the first to show the relationship between preceding maternal
347 depressive/anxious symptoms and an increased children's tic frequency two years later in early
348 adolescence. Furthermore, we found longitudinal bidirectional relationships between maternal
349 depressive/anxious symptoms and children's tic frequency. Although we could not separate
350 environmental factors and genetic factors in this research, the findings implied that it may be important
351 to care not only for children with tics but also for their mothers' depressive/anxious symptoms when
352 tics are treated in early adolescence.

353 **Conflict of Interest**

354 The authors declare that the research was conducted in the absence of any commercial or financial
355 relationships that could be construed as a potential conflict of interest.

356 **Author Contributions**

357 TY conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised
358 the manuscript, being supervised by SA. AN, SY, YK and KK critically reviewed the manuscript for
359 important intellectual content and contributed to the discussion. SU supervised the statistical analysis.
360 All authors contributed to and have approved the final manuscript.

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371 **List of abbreviations**

- 372 ADHD: attention-deficit/hyperactivity disorder
- 373 CFI: comparative fit index
- 374 CI: confidence interval
- 375 CT: chronic tic disorder
- 376 DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5th edition
- 377 GHQ-28: General Health Questionnaire-28
- 378 K6: Kessler Psychological Distress Scale
- 379 OCD: obsessive-compulsive disorder
- 380 RMSEA: root mean square error of approximation
- 381 SD: standard deviation
- 382 TS: Tourette syndrome
- 383 TTC: Tokyo Teen Cohort

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386

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558 York: The Guilford Press; 2012. p. 265-278.

559 **Table 1 Demographic characteristics of the participants**

Variables	T1 (10 years of age)		T2 (12 years of age)	
	<i>n</i> / <i>Mean</i>	<i>(%)</i> / <i>SD</i>	<i>n</i> / <i>Mean</i>	<i>(%)</i> / <i>SD</i>
Sex, male	1,684	(53.1%)		
Age in months	122.1	3.3	146.0	3.7
Maternal age	42.0	4.2		
Family income ^{a)}				
< 5 million yen	620	(20.4%)	448	(16.5%)
≥ 5 million yen, < 8 million yen	941	(31.0%)	782	(28.8%)
≥ 8 million yen, < 10 million yen	568	(18.6%)	518	(19.1%)
≥ 10 million yen	917	(30.1%)	970	(35.7%)
Maternal alcohol use during pregnancy	748	(27.2%)		
Tic frequency				
no tics	2,365	(76.7%)	2,042	(76.5%)
with tics	720	(23.3%)	626	(23.5%)
less than once a month	138	(4.5%)	122	(4.6%)
1-3 times a month	114	(3.7%)	115	(4.3%)
about once a week	37	(1.2%)	66	(2.5%)
more than once a week	206	(6.7%)	161	(6.0%)
every day	225	(7.3%)	162	(6.1%)
Maternal depressive/anxious symptoms				
T1, K6	2.9	3.3		
T2, GHQ-28			5.4	4.9

Abbreviations: SD, standard deviation; K6, Kessler Psychological Distress Scale; GHQ-28, General Health Questionnaire-28.

a) Family income was evaluated on the 11-point scale described in the Materials and Method section and categorized into the four groups in this table.

Table 2 Relationships between maternal depressive/anxious symptoms and children’s tic frequency (N = 3,171)

Path	Unadjusted model						Adjusted model					
	β	B	SE	95% CI		<i>p</i> value	β	B	SE	95% CI		<i>p</i> value
Maternal Depressive/Anxious Symptoms T1 \Leftrightarrow Children’s Tic Frequency T1	.10	.50	.10	.31	- .70	<.001	.09	.49	.10	.30	- .69	<.001
Maternal Depressive/Anxious Symptoms T2 \Leftrightarrow Children’s Tic Frequency T2	.09	.52	.12	.28	- .75	<.001	.08	.50	.12	.26	- .73	<.001
Maternal Depressive/Anxious Symptoms T1 \rightarrow Maternal Depressive/Anxious Symptoms T2	.47	.69	.03	.09	- .74	<.001	.46	.68	.03	.63	- .73	<.001
Children’s Tic Frequency T1 \rightarrow Children’s Tic Frequency T2	.41	.39	.02	.35	- .42	<.001	.40	.38	.02	.35	- .41	<.001
Maternal Depressive/Anxious Symptoms T1 \rightarrow Children’s Tic Frequency T2	.06	.03	.01	.01	- .05	<.001	.06	.03	.01	.01	- .04	<.001
Children’s Tic Frequency T1 \rightarrow Maternal Depressive/Anxious Symptoms T2	.07	.20	.05	.10	- .30	<.001	.06	.19	.05	.09	- .30	<.001
$\chi^2 = 0$, Degrees of freedom = 0, <i>p</i> = -, CFI = 1.0, RMSEA = 0 (saturated model)						$\chi^2 = 77.834$, Degrees of freedom = 10, <i>p</i> < .001, CFI = .950, RMSEA = .046						

Abbreviations: T1, 10 years of age; T2, 12 years of age; β , standardized coefficient; B, coefficient; SE, standard error; CI, confidence interval; CFI, comparative fit index; RMSEA, root mean square error of approximation.

564 **Figure 1 Flowchart of participant recruitment.**

565

566 **Figure 2 Cross-lagged model of relationships between maternal depressive/anxious symptoms**
567 **and children's tic frequency.** Note: This figure shows the results of the adjusted model in Table 2.
568 Paths from covariates are omitted from the figure. Abbreviations: e, error variable; T1, 10 years of
569 age; T2, 12 years of age. *** $p < .001$

Figures

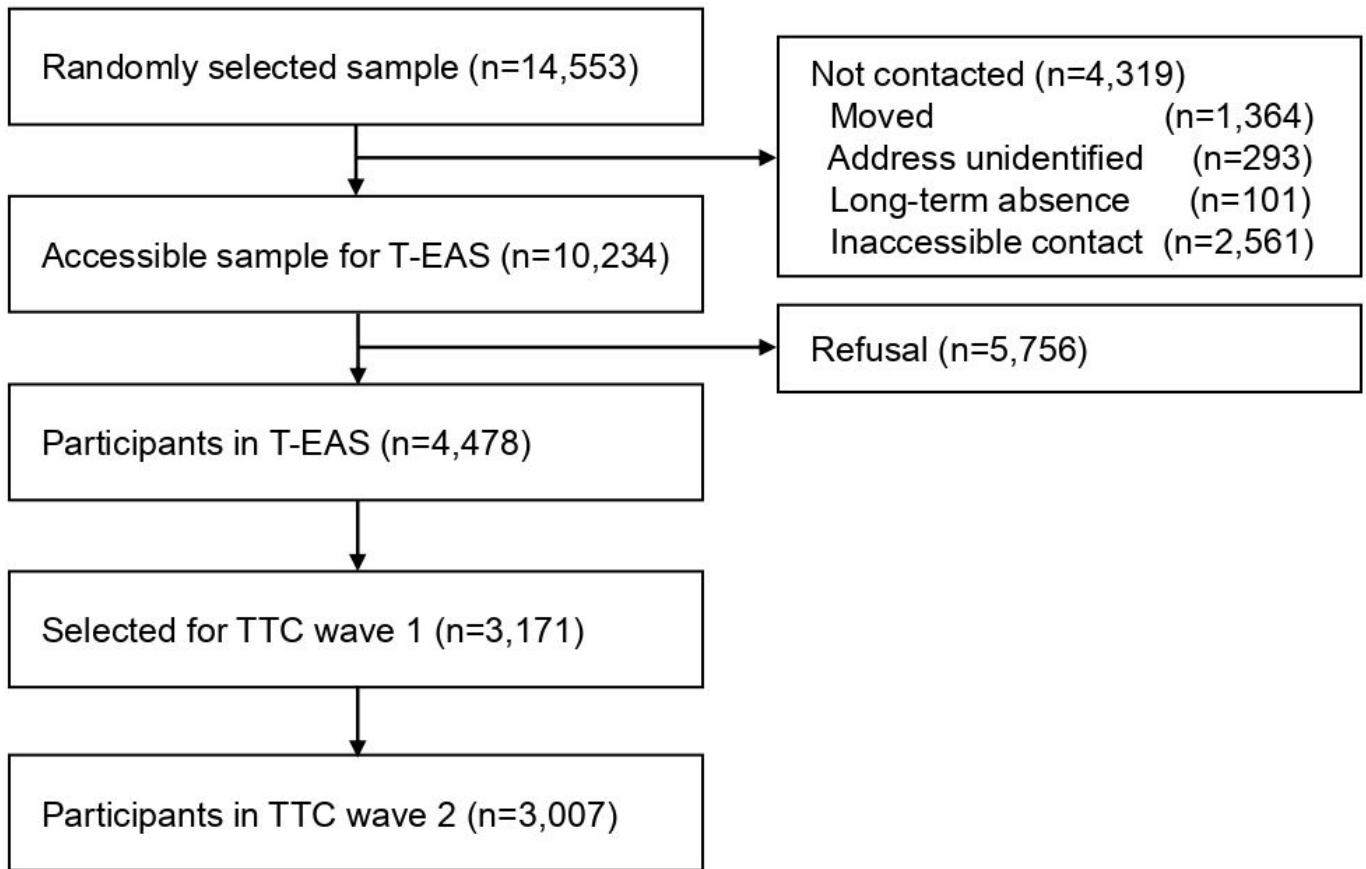


Figure 1

Flowchart of participant recruitment.

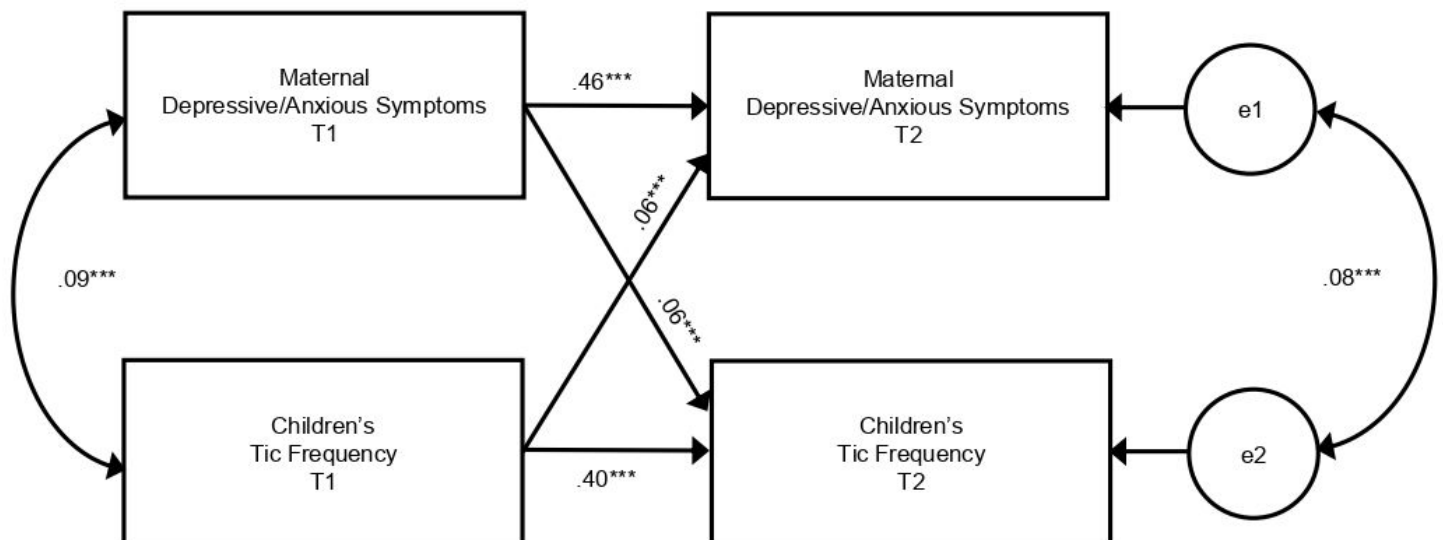


Figure 2

Cross-lagged model of relationships between maternal depressive/anxious symptoms and children's tic frequency. Note: This figure shows the results of the adjusted model in Table 2. Paths from covariates are omitted from the figure. Abbreviations: e, error variable; T1, 10 years of age; T2, 12 years of age. *** $p < .001$

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