Supplementary Online Content

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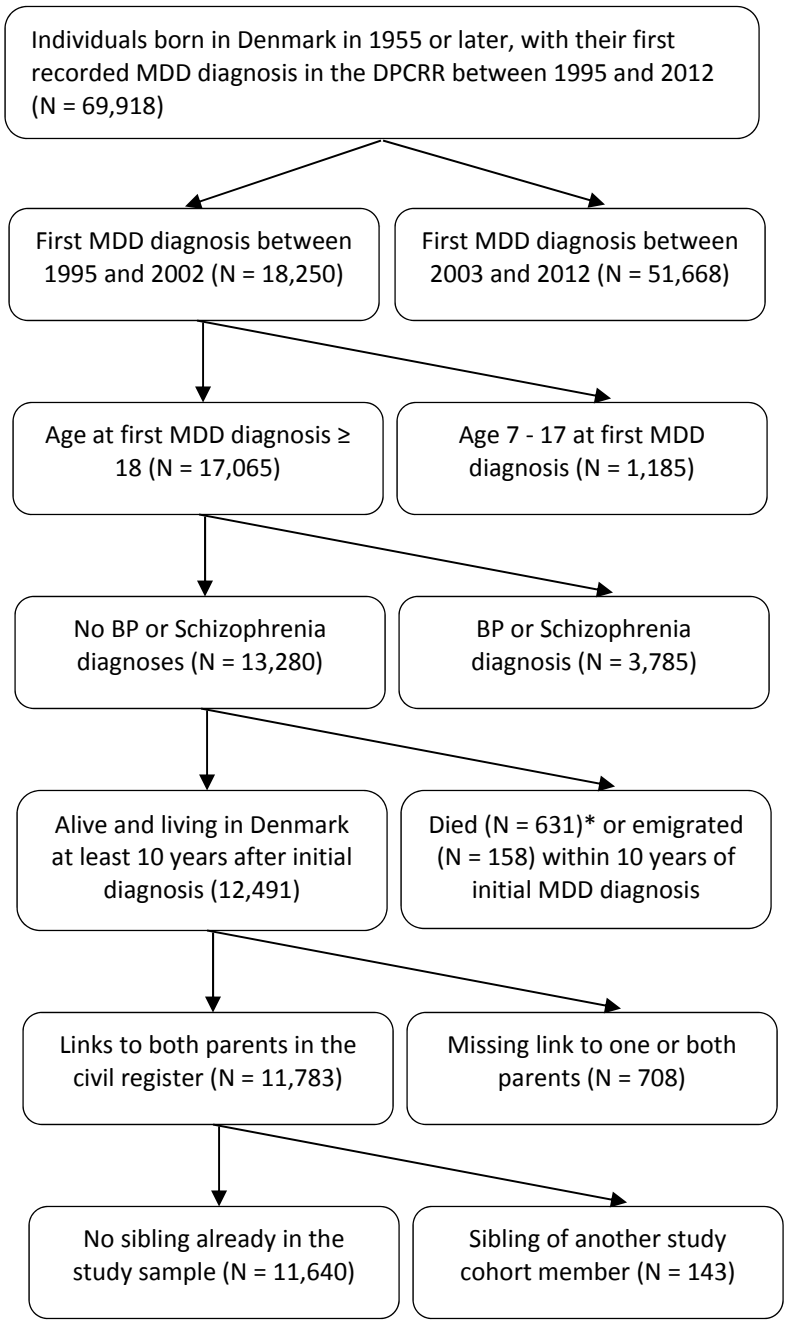
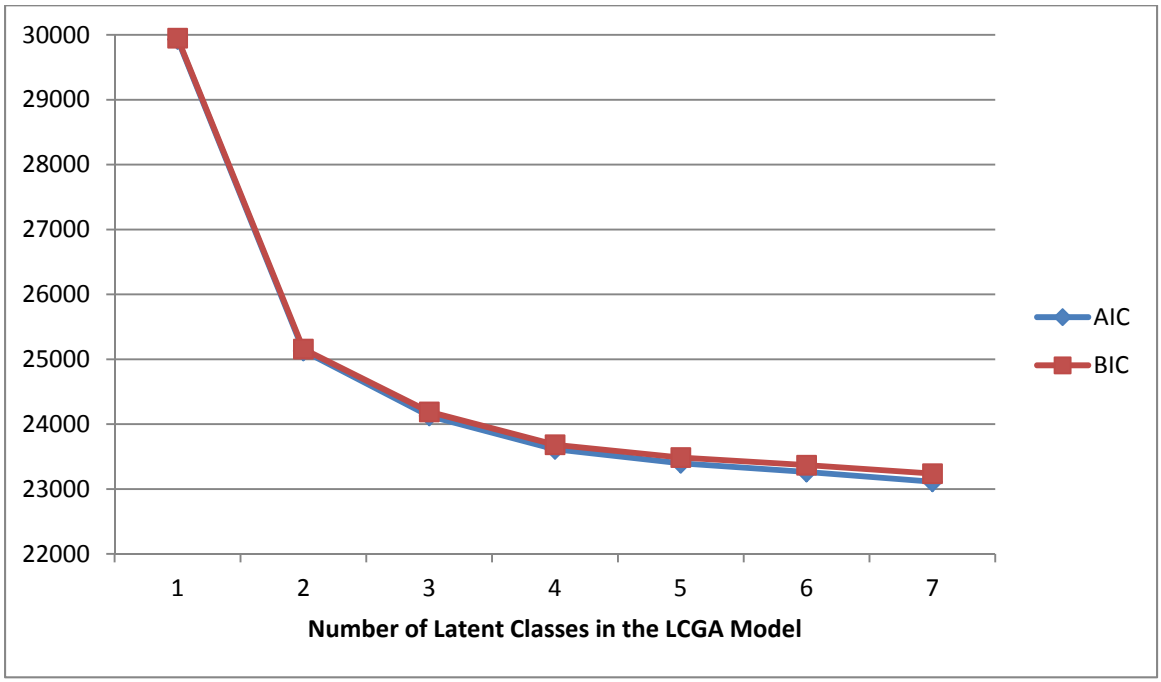
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Sample Selection Pipeline

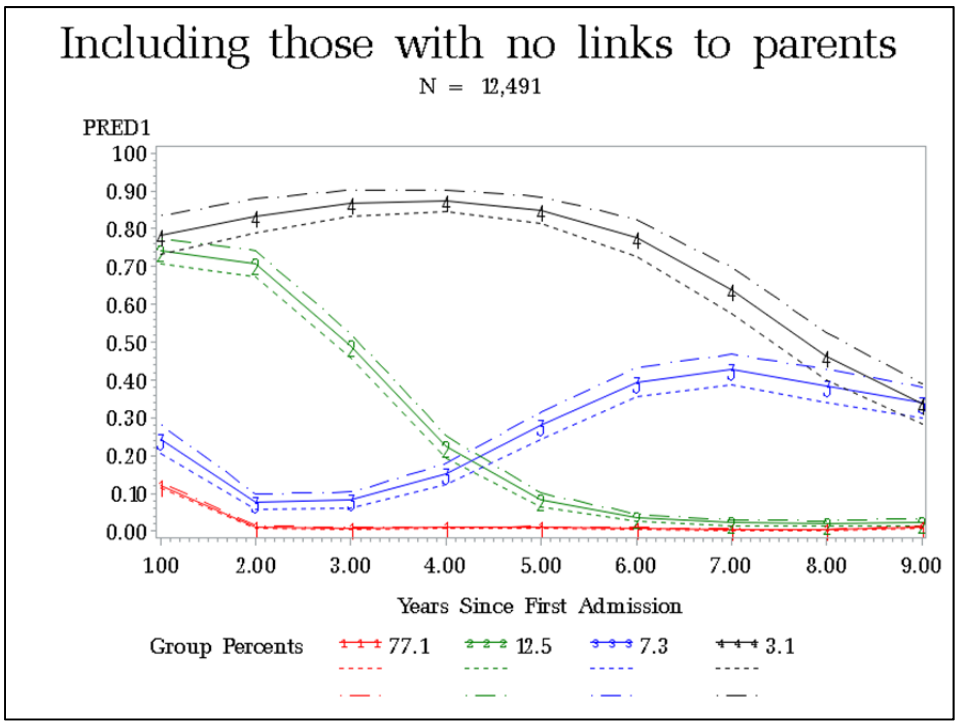


*Individuals who died within 10 years of their initial MDD diagnosis were older at first recorded MDD diagnosis (M = 35.2, SD = 7.4) and more likely to be male (56.5%). The most common causes of death were intentional self-harm (30.1%) and accidents (11.3%).

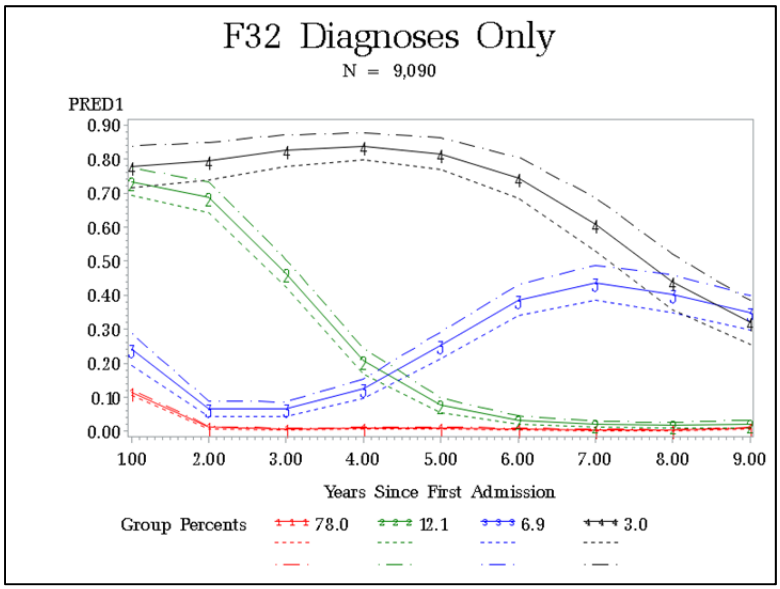
eFigure 2. Scree-like Plot of AIC and BIC Values



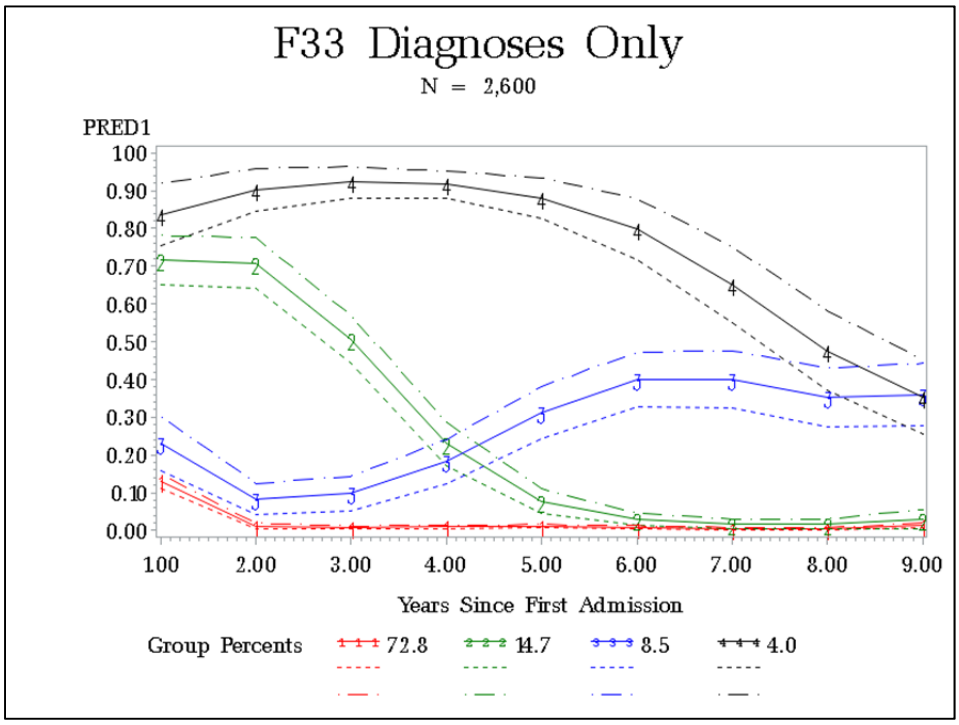
eFigure 3. Trajectory Patterns in the Sample Including Individuals With No Links to Parents in the Civil Register Who Otherwise Meet Criteria for Inclusion (N =12,491)



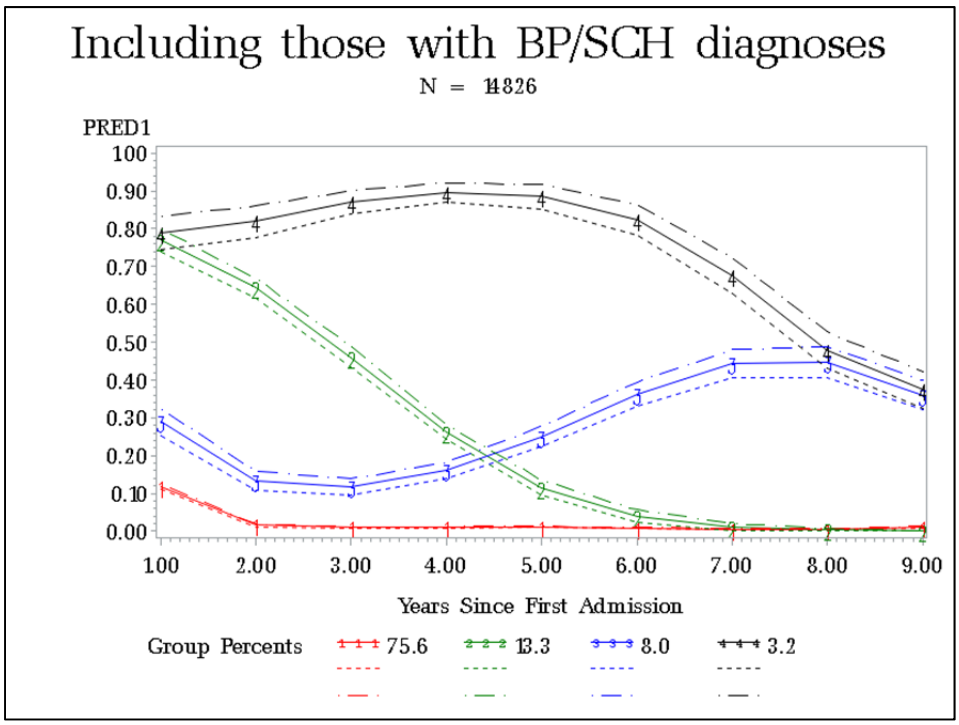
eFigure 4. Trajectory Patterns in Sample Members With F32 as Their First Recorded MDD Diagnosis



eFigure 5. Trajectory Patterns in Members of the Sample With F33 as Their First Recorded MDD Diagnosis



eFigure 6. Trajectory Patterns in the Sample Including Individuals Who Also Received a Bipolar or Schizophrenia Spectrum Diagnosis



eResults. Sensitivity Analyses

A) Links to parents

One of the goals in this study was to examine the relationship between parental history of psychiatric diagnoses and MDD trajectory. To do this, we needed individuals we could successfully link to parents using the Danish registries. Around 2% of the Danish population is missing links to parents because the parent (usually the father) is unknown; however the vast majority of individuals who are missing links to parents in the register are older individuals who were adults when the register was established in 1968. Links to parents in the registers are most accurate for individuals born in 1970 or later, 2 years after the civil register was first established (Pedersen et al., 2006).[1]

In an effort to balance our need for accurate information on links to parents with our desire for a representative sample, we selected individuals into our study sample if they a) were born in 1955 or later and therefore no more than 13 when the register was established in 1968 and b) were not missing links to parents for other reasons. Among those excluded for missing links to parents, 96.5% were born between 1955 and 1970.

To determine the extent to which this criterion influenced the representativeness of our results, we conducted a sensitivity analysis in which we examined trajectories and predictors/correlates of trajectories (besides parental disorders) in the sample of individuals born in 1955 or later but without reference to links to parents. Because we could not link to parents, we were also unable to exclude siblings. Results of this sensitivity analyses are shown in eTable 1 and eFigure 3. The sample contained 12,491 individuals.

The results of this sensitivity analysis suggest that excluding individuals without links to parents in the civil register did not impact the extent to which the results are generalizable to individuals born in Denmark in 1955 or later with their first recorded MDD diagnosis between 1995 and 2002 who were alive and living in Denmark at least 10 years after their initial recorded MDD diagnosis. Both trajectory patterns and associations with predictors/correlates are virtually identical to the main analyses.

B) Prevalence bias

Prevalence bias occurs when a sample contains a mix of incident (i.e. first-onset) and prevalent (i.e. not first onset) cases, and being a prevalent case is associated somehow with the outcome of interest. Individuals who have already had a previous depression episode are known to be more likely to experience a recurrent episode (e.g. Kessing et al., 1999),[2] therefore assessments of course in an MDD sample with a mix of incident and prevalent cases will be subject to prevalence bias.

We attempted to reduce prevalence bias in our sample by excluding individuals with a record of inpatient treatment for MDD before 1995. We were unable to exclude individuals with previous outpatient treatment before 1995, as these visits were not recorded in the register at that time; therefore residual prevalence bias is a still a concern. To assess the impact of residual prevalence bias, we ran the trajectories model separately in individuals whose first recorded MDD diagnosis was F32

'single depressive episode' (N = 9090) and individuals whose first MDD diagnosis was F33 'recurrent depression' (N = 2,600). It should be noted, however, that past research suggests that around 11.4% of people who receive an 'F32' diagnosis in the DPCRR actually have recurrent depression (Bock et al., 2009),[3] therefore even this sensitivity analyses does not completely eliminate the possibility of prevalence bias. To our knowledge, there are no estimates of the proportion of individuals who receive an F33 diagnosis in the register who are actually first-onset MDD cases.

Results among individuals with F32 as their first recorded MDD diagnosis in the DPCRR are shown in eTable 2 and eFigure 4. Overall, differences between the trajectory patterns in this sensitivity analysis and those of the main analyses were negligible. Although very small, these differences were in the expected direction: Class 1 was slightly larger, classes 2, 3 and 4 were slightly smaller which is consistent with the idea that prevalent cases have a course characterized by greater risk of recurrence.

In terms of predictors/correlates, the effects of gender, inpatient treatment, past recorded suicide attempt/self-harm, illness severity and parental psychiatric diagnoses were in line with those of the main analysis. Significant effects for birth year, calendar year at first MDD diagnosis and rural birth place suggest a greater influence of secular and geographic trends in this group.

Next we examined trajectories in individuals who received an F33 diagnosis first. The results are shown in eTable 3 and eFigure 5. Again, differences in trajectory patterns were small, but in the expected direction: Class 1 was smaller; classes 2, 3 and 4 were bigger. Many of the correlates were no longer significant, which is likely due to decreased statistical power as in many cases, the effect sizes themselves are similar in magnitude.

The results of these sensitivity analyses confirm the presence of residual prevalence bias in our sample, but suggest that the impact of this bias is small.

C) Conditioning on the future

It is relatively common in the DPCRR for individuals who receive an MDD diagnosis to subsequently receive a bipolar or schizophrenia spectrum diagnosis. In this study, we wanted a sample of truly unipolar cases (as opposed to individuals in the depression stage of a bipolar illness, for example), therefore we excluded individuals who received a bipolar or schizophrenia diagnosis in the DPCRR. However in doing so, we conditioned on a future event. Conditioning on the future can introduce bias, therefore to assess the impact of any potential bias we conducted a sensitivity analyses where we examined trajectories in a sample of MDD cases without excluding those who also received a bipolar or schizophrenia diagnosis. Results of this sensitivity analyses are shown in eTable 4 and eFigure 6. The sample included 14,826 individuals. Again, differences between the results of this sensitivity analyses and those of the main analysis were minor, which suggests that including these individuals would not have led us to make any different conclusions about MDD trajectories. The small differences are again in the expected direction - class 1 was slightly smaller, classes 2, 3 and 4 were slightly bigger. This suggests that people who go on to develop bipolar or schizophrenia spectrum disorders receive more MDD treatment, at least until their diagnosis shifts.

eReferences

1. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The danish civil registration system: a cohort of eight million persons. Danish Medical Bulletin. 2006;53(4):441-449.
2. Kessing LV, Andersen PK. The effect of episodes on recurrence in affective disorder: a case register study. J Affect Disord. 1999;53:225-231.
3. Bock C, Bukh JD, Vinberg M, Gether U, Kessing LV. Validity of the diagnosis of a single depressive episode in a case register. Clin Pract Epidemiol Ment Health. 2009;5:4.

eTable1. Characteristics of the Sample Including Individuals With No Links to Parents in the Civil Register Who Otherwise Meet Criteria for Inclusion (N =12,491)

	Total sample (N = 12,491)	Prolonged initial contact vs. Brief contact			Later re-entry vs. Brief contact			Persistent contact vs. Brief contact		
	N (%)	OR	LCL	UCL	OR	LCL	UCL	OR	LCL	UCL
Gender	8107 (64.9)	1.81	1.57	2.09	1.34	1.11	1.61	2.03	1.55	2.64
Age at first MDD diagnosis (M, SD)	31.9 (7.5)	1.01	0.88	1.17	0.98	0.82	1.16	1.05	0.89	1.25
Inpatient treatment at first visit for MDD	3116 (25.0)	1.46	1.26	1.68	1.46	1.21	1.77	1.17	0.90	1.52
Previous recorded suicide attempt/self-harm	1625 (13.0)	0.76	0.62	0.94	1.14	0.90	1.44	0.91	0.65	1.28
Moderate severity	5745 (46.0)	1.61	1.35	1.92	1.78	1.42	2.23	1.60	1.18	2.17
Severe without psychotic feature	1510 (12.1)	2.19	1.75	2.73	1.89	1.40	2.54	2.01	1.35	2.99
Severe with psychotic features	350 (2.8)	3.06	2.18	4.30	1.42	0.80	2.51	2.76	1.53	5.00
Severity unspecified	1826 (14.6)	1.33	1.06	1.67	0.97	0.70	1.36	0.99	0.64	1.52
Birth year	1955-1984	1.00	0.86	1.15	0.99	0.83	1.18	1.02	0.87	1.21
Calendar year at first diagnosis	1995-2002	0.98	0.84	1.13	1.03	0.86	1.23	0.94	0.80	1.11
Rural birth place	2834 (22.7)	1.09	0.94	1.26	1.19	0.98	1.45	1.42	1.11	1.82

OR = odds ratio, LCL = lower 95% confidence limit, UCL = upper 95% confidence limit. Numbers in red are significant at the p = .05 level.

eTable 2. Characteristics of Members of the Sample With F32 as Their First Recorded MDD Diagnosis

Characteristic	Total sample (N = 9,090)	Prolonged initial contact vs. Brief contact			Later re-entry vs. Brief contact			Persistent contact vs. Brief contact		
	N (%)	OR (95% CI)			OR (95% CI)			OR (95% CI)		
Gender	5760 (63.4)	1.97	1.66	2.34	1.52	1.21	1.91	2.05	1.51	2.79
Age at first MDD diagnosis	31.2 (7.3)	1.18	1.04	1.34	1.13	1.00	1.27	1.07	0.82	1.39
Inpatient treatment at first visit for MDD	2316 (25.5)	1.62	1.37	1.92	1.31	1.03	1.66	1.34	0.99	1.81
Previous recorded suicide attempt/self harm	1153 (12.7)	0.70	0.54	0.90	1.16	0.88	1.55	0.86	0.57	1.31
Moderate severity	4188 (46.1)	1.72	1.40	2.12	2.04	1.55	2.68	1.62	1.12	2.35
Severe without psychotic feature	1063 (11.7)	2.49	1.90	3.25	2.12	1.46	3.07	2.54	1.59	4.06
Severe with psychotic features	274 (3.0)	2.99	2.00	4.48	2.01	1.07	3.75	2.93	1.49	5.74
Severity unspecified	1275 (14.0)	1.18	0.88	1.58	1.13	0.76	1.69	1.25	0.76	2.07
Parental major depression	1023 (11.3)	0.92	0.70	1.20	1.67	1.26	2.23	1.21	0.80	1.84
Parental bipolar disorder	204 (2.2)	1.38	0.85	2.23	1.40	0.71	2.76	0.84	0.33	2.17
Parental schizophrenia and related disorders	348 (3.8)	1.28	0.87	1.88	0.79	0.42	1.47	2.59	1.55	4.32
Parental substance abuse	770 (8.5)	0.79	0.58	1.07	0.94	0.65	1.35	1.14	0.70	1.86
Parental anxiety/somatic disorders	1198 (13.2)	1.33	1.05	1.67	1.26	0.94	1.69	0.79	0.49	1.26
Birth year	1955-1984	1.17	1.03	1.32	1.15	1.02	1.29	1.04	0.80	1.35
Calendar year at first diagnosis	1995-2002	0.84	0.74	0.95	0.91	0.80	1.04	0.95	0.73	1.25
Rural birth place	2047 (22.5)	1.08	0.90	1.29	1.29	1.03	1.63	1.49	1.11	2.00

OR = odds ratio, LCL = lower 95% confidence limit, UCL = upper 95% confidence limit. Numbers in red are significant at the p = .05 level.

eTable 3. Characteristics of Members of the Sample With F33 as Their First Recorded MDD Diagnosis

Characteristic	Total sample (N = 2,600)	Prolonged initial contact vs. Brief contact			Later re-entry vs. Brief contact			Persistent contact vs. Brief contact		
	N (%)	OR (95% CI)			OR (95% CI)			OR (95% CI)		
Gender	1764 (67.9)	1.45	1.08	1.94	1.11	0.76	1.60	2.36	1.37	4.06
Age at first MDD diagnosis	32.4 (7.1)	0.73	0.57	0.92	0.83	0.65	1.05	1.01	0.67	1.51
Inpatient treatment at first visit for MDD	588 (22.6)	1.16	0.84	1.59	1.57	1.06	2.32	0.84	0.49	1.42
Previous recorded suicide attempt/self-harm	328 (12.6)	0.76	0.50	1.15	0.96	0.57	1.63	0.91	0.47	1.76
Moderate severity	1179 (45.5)	1.43	0.99	2.06	1.36	0.86	2.16	2.06	1.13	3.73
Severe without psychotic feature	336 (12.9)	1.38	0.86	2.23	1.37	0.76	2.49	1.78	0.83	3.86
Severe with psychotic features	60 (2.3)	4.19	2.06	8.53	0.72	0.15	3.48	2.08	0.47	9.20
Severity unspecified	434 (16.7)	1.30	0.84	2.00	0.69	0.35	1.33	0.59	0.23	1.51
Parental major depression	324 (12.5)	1.45	0.99	2.12	1.59	0.99	2.58	1.09	0.54	2.21
Parental bipolar disorder	59 (2.3)	0.48	0.15	1.54	1.88	0.77	4.59	1.08	0.24	4.83
Parental schizophrenia and related disorders	85 (3.3)	0.78	0.36	1.71	0.79	0.30	2.09	2.47	0.95	6.41
Parental substance abuse	223 (8.6)	1.29	0.80	2.06	0.97	0.53	1.79	0.41	0.12	1.34
Parental anxiety/somatic disorders	308 (11.9)	1.43	0.96	2.12	1.41	0.86	2.32	0.75	0.31	1.79
Birth year	1955-1984	0.71	0.56	0.91	0.82	0.65	1.04	0.96	0.64	1.45
Calendar year at first recorded diagnosis	1995-2002	1.35	1.05	1.74	1.18	0.92	1.51	0.95	0.63	1.43
Rural birth place	595 (22.9)	1.15	0.85	1.57	1.04	0.69	1.57	1.07	0.65	1.76

OR = odds ratio, LCL = lower 95% confidence limit, UCL = upper 95% confidence limit. Numbers in red are significant at the p = .05 level, numbers in purple have p values less than .10.

eTable 4. Characteristics of the Sample Including Individuals Who Also Received a Bipolar or Schizophrenia Spectrum Diagnosis

Characteristic	Total sample (N = 14,826)	Prolonged initial contact vs. Brief contact			Later re-entry vs. Brief contact			Persistent contact vs. Brief contact		
	N (%)	OR (95% CI)			OR (95% CI)			OR (95% CI)		
Gender	9323 (62.9)	1.77	1.56	2.01	1.59	1.35	1.87	1.96	1.56	2.46
Age at first MDD diagnosis	31.3 (7.3)	1.08	0.97	1.20	1.03	0.86	1.24	0.93	0.82	1.07
Inpatient treatment at first visit for MDD	4049 (27.3)	1.54	1.36	1.75	1.43	1.22	1.69	1.28	1.02	1.61
Previous recorded suicide attempt/self harm	2056 (13.9)	0.66	0.55	0.80	1.20	0.98	1.46	0.93	0.69	1.25
Moderate severity	6669 (45.0)	1.60	1.36	1.88	1.67	1.37	2.04	1.77	1.32	2.37
Severe without psychotic feature	1873 (12.6)	2.11	1.73	2.58	1.70	1.31	2.21	2.20	1.53	3.16
Severe with psychotic features	724 (4.9)	2.45	1.89	3.18	1.58	1.09	2.29	2.15	1.33	3.48
Severity unspecified	2189 (14.8)	1.19	0.96	1.47	1.04	0.79	1.38	1.19	0.81	1.76
Parental major depression	1826 (12.3)	1.14	0.96	1.37	1.54	1.25	1.88	1.24	0.92	1.69
Parental bipolar disorder	410 (2.8)	1.29	0.92	1.81	1.41	0.92	2.14	1.24	0.70	2.19
Parental schizophrenia and related disorders	671 (4.5)	1.13	0.86	1.49	1.01	0.71	1.45	2.13	1.45	3.14
Parental substance abuse	1308 (8.8)	0.85	0.68	1.06	0.88	0.68	1.15	0.83	0.56	1.23
Parental anxiety/somatic disorders	2001 (13.5)	1.18	0.99	1.41	1.21	0.97	1.50	0.86	0.61	1.21
Birth year	1955 - 1984	1.06	0.96	1.18	1.03	0.86	1.25	0.90	0.79	1.03
Calendar year at first recorded diagnosis	1995-2002	0.91	0.82	1.02	0.97	0.80	1.17	1.06	0.92	1.23
Rural birth place	3277 (22.1)	1.09	0.95	1.25	1.15	0.97	1.37	1.18	0.93	1.49

OR = odds ratio, LCL = lower 95% confidence limit, UCL = upper 95% confidence limit. Numbers in red are significant at the p = .05 level.

