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Is familial risk for depression confounded by individual and familial socioeconomic factors and neighborhood environmental factors? A 7-year follow-up study in Sweden

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Abstract

Family history of depression is an important risk factor for depression. The aim of this study was to examine whether the effect of family history of depression is confounded by individual and familial socioeconomic factors (i.e., country of origin, educational attainment, family income and mobility) and neighborhood environmental factors (i.e., neighborhood deprivation and neighborhood social capital). The study population comprised 188,907 individuals aged 20–44 years from a nationwide sample of primary care centers in Sweden. Among these individuals, 22,014 with a first event of depression (6,486 men and 15,528 women) were identified during the 7-year follow-up period. Family history of depression was defined as depression in at least one parent. Cross-classified multilevel logistic regression models were used to calculate odds ratios with 95% credible intervals. Increased familial odds were observed after adjustment for individual and familial socioeconomic factors and neighborhood environmental factors for both men and women. Our results suggest that family history of depression is an independent risk factor for depression. Offspring of parents with depression are important targets for disease prevention, regardless of individual and familial socioeconomic factors and neighborhood environmental factors.

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Conflicts of interest

None.

Keywords

depression; familial risk; follow-up study; multilevel analysis

1. Introduction

Depression is a common mental disorder and the proportion of the global population with depression in 2015 is estimated to be 4.4% (World Health Organization, 2017). Many studies have revealed risk factors related to depression, including socioeconomic factors (e.g., educational attainment and income), physical inactivity, and other health-related factors, e.g., current history of the disease (Tani et al., 2016; Mammen et al., 2013; Huang et al., 2010). It is also important to note that family history of depression is an important risk factor for depression (Levinson, 2006).

A review and meta-analysis of the genetic epidemiology in major depression has indicated that major depression is considered a familial disorder, which mostly or entirely results from genetic influences (Sullivan et al., 2000). There are now numerous established twin studies, indicating the heritability of major depression (Kendler et al., 2006; Dunn et al., 2015). In addition, genome-wide studies were able to identify risk loci (CONVERGE consortium, 2015; Hyde et al., 2016). For a deeper understanding of the etiology of depression, it is necessary to construct a model that considers individual, familial, and environmental factors simultaneously to reveal the potential influence of these factors (Avenevoli and Merikangas, 2006; Mitjans et al., 2012; Dunn et al., 2015).

The social determinants of depression have been investigated in several studies. A previous meta-analysis found that lower socioeconomic factors (e.g., educational attainment and family income) were associated with a higher risk of depression (Lorant et al., 2003). Similar to socioeconomic factors at the individual and familial level, the neighborhood environment (e.g., neighborhood deprivation and neighborhood social capital) could also play an important role in the development of depression (Lofors and Sundquist, 2007; Richardson et al., 2015). To our knowledge, no large-scale follow-up study has yet examined the effect of familial depression, individual and familial socioeconomic factors, and neighborhood environmental factors, simultaneously.

The first aim of this large-scale 7-year follow-up study was to examine the association between family history of depression and depression. The second aim was to examine whether the familial risk for depression remains significant after adjustment for individual and familial socioeconomic factors (i.e., country of origin, educational attainment, family income, and mobility) and neighborhood environmental factors (i.e., neighborhood deprivation and neighborhood social capital).

2. Methods

2.1. Participants

The study population comprised 80,072 men and 108,835 women from a nationwide sample of primary care centers in Sweden. The data used in this study were retrieved from national

registers (Mezuk et al., 2013; Sundquist et al., 2011). Complete medical records were obtained from a nationally representative sample of 75 primary healthcare centers beginning on January 1, 2001. These records were then linked to national inpatient (available from 1964), outpatient (available from 2001), and prescription drug (available from 2005) registries provided by the National Board of Health and Welfare. Additional linkages were performed using several national Swedish data registers, including but not limited to the following: the Swedish national population and housing census (1960–1990), the total population register, the multi-generation register, and the cause of death register. These registers contain individual-level information on, for example, the following factors: age, sex, parents, siblings, children, occupation, education, region of residence, hospital diagnoses, and dates of hospital admissions for the period 1964–2010. The registers also include information on country of origin, date of emigration, and date and cause of death. In the Multi-Generation register, offspring born in Sweden since 1932 are linked to their parents. All linkages were performed using an individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for analysis to ensure anonymity of individuals. The quality and validity of primary care electronic medical records in Sweden is high (Grimsmo et al., 2001; Nilsson et al., 2003). The participants were restricted to individuals aged 20–44 years by January 1, 2001, and followed until onset of depression, death, or censoring at the end of the study period, on December 31, 2007.

2.2. Measures

2.2.1. Depression—Depression was defined as a clinical diagnosis from primary care, inpatient, or outpatient registries (ICD-10 code F32) in the time from January 1, 2001, to the end of the follow-up period. Depression was assessed as a binary indicator (never diagnosed with depression vs. diagnosed with depression at least once in any healthcare setting) for analysis. To ensure that all depression cases were new, we excluded those individuals in the study population (offspring) with pre-existing depression. However, parents with prevalent depression were not excluded. We identified 22,014 depression cases (6,486 men and 15,528 women) during the follow-up period.

2.2.2. Family history of depression—Family history of depression was assessed as a diagnosis of depression (ICD-10 code F32) in either biological parent from January 1, 2001, to December 31, 2007, from the primary care, outpatient, and inpatient registries, and the prescription drug registry (ATC code N06A).

2.2.3. Individual and familial socioeconomic factors—Educational attainment was categorized as completion of compulsory school or less (≤ 9 years or missing), practical high school, or some theoretical high school (10–11 years), and completion of theoretical high school or college (≥ 12 years). Country of origin was classified as Swedish-born or foreign-born; the latter was based on the most common immigrant groups in Sweden, which resulted in the following groups: (1) Swedish-born, (2) born in Finland, (3) born in Western Europe or North America (e.g., Denmark, United Kingdom, France, Italy, Germany, and United States), (4) born in Eastern Europe (e.g., Bosnia–Herzegovina, former Yugoslavia, Czechoslovakia, Poland, Romania, and Russia), (5) born in the Middle East (e.g., Turkey,

Lebanon, Iran, Iraq, and Morocco), and (6) all other nativities. Family income was based on the annual family income divided by the number of people in the family (i.e., individual family income per capita) as calculated by Statistics Sweden. The income calculation was weighted, taking the ages of the family members into account. For example, children were given lower consumption weights than adults. The calculation was performed as follows: the sum of all family members' incomes was multiplied by the individual's consumption weight divided by the family members' total consumption weight. The final variable was calculated as empirical quartiles from the distribution and classified as low, middle-low, middle-high, and high. Mobility was included to partly account for length of time lived in the neighborhood, categorized as moved/not moved between Jan 1st 2001 and Dec 31st 2006.

2.2.4. Neighborhood environmental factors—Neighborhoods were defined on the basis of *small areas for market statistics* (SAMS), which are small geographical units with boundaries defined by homogenous types of buildings as defined by Statistics Sweden. All Swedish individuals have been geocoded to these areas. There are approximately 9,200 SAMS throughout Sweden, with an average population of 1,000 individuals. SAMS were used as proxies for neighborhoods, as in previous research (Calling et al., 2016; Li et al., 2016; Sundquist, K., et al., 2014). In total, this study included 188,907 individuals, nested in 4,703 neighborhoods.

We identified deprivation indicators used by previous studies to characterize neighborhood environment, and performed principal component analysis to select deprivation indicators in the Swedish national database. Four variables were selected for those aged 25–64 years: low education level (< 10 years of formal education), low income (income from all sources, including that from interest and dividends < 50% of the median individual income), unemployment (excluding full-time students, those completing military service, and early retirees), and receipt of social welfare. Each variable loaded on the first principal component with similar loadings (+ 0.47 to + 0.53) and explained 52% of variation between these variables. A z-score was calculated for each SAMS. The z scores, weighted by the coefficients for the eigenvectors, were then summed to create the index (Gilthorpe, 1995). The index was categorized into three groups: < 1 standard deviation (SD) from the mean (low deprivation), > 1 SD from the mean (high deprivation), and within 1 SD of the mean (moderate deprivation). Higher scores reflected more deprived neighborhoods, as depicted in previous studies (Winkleby et al., 2007).

Neighborhood social capital was also included in the analysis. This variable was measured as the number of people in the neighborhood who voted in local government elections divided by the number of people in the neighborhood who were entitled to vote, as previous studies have done (Sundquist, J., et al., 2014; Sundquist, K., et al., 2014). Neighborhoods were divided into the following three groups based on the proportion of residents who voted: (1) low, (2) intermediate, and (3) high. Group 1 comprised 20% of neighborhoods with lowest proportions of voters (≤ 74.0%); group 2 comprised 60% of neighborhoods with intermediate proportions of voters (74.1–82.0%); and group 3 comprised 20% of neighborhoods with the highest proportions of voters (> 82.0%).

2.3. Statistical analyses

We analyzed the data using cross-classified multilevel logistic regression models to account for the family and neighborhood clustering (Snijders and Bosker, 1999). This means that the family clusters, in this sample corresponding to full siblings, and neighborhood clusters are included as random effects in the model while the individual, family and neighborhood variables are included as fixed effects. Accounting for family clustering only resulted in minor changes of the estimates. We present the results as odds ratios (ORs) with 95% credible intervals (CIs). Three consecutive cross-classified models were fitted: *Model 1* only included family history of depression; *Model 2* included family history of depression, neighborhood social capital, and neighborhood deprivation; and *Model 3*, that is, the full model, included family history of depression, neighborhood environmental factors (i.e., neighborhood social capital and neighborhood deprivation), and individual and familial socioeconomic factors (i.e., educational attainment, country of origin, family income and mobility). Data for men and women were analyzed in separate models. We also tested for interactions between the variables within each level as well as between the variables between each level (cross-level interactions). The analyses were performed using MLwiN version 2.27 and the Markov Chain Monte Carlo (MCMC) technique was used to obtain all parameter-estimates.

2.4. Ethical considerations

This study was approved by the Ethics Committee of Lund University, Sweden. Approval to link and analyze the data used in the present study was granted to us from Statistics Sweden, the National Board of Health and Welfare, the Ethical Review Board, and The Swedish Data Protection Authority in Sweden. All data analyses were conducted in Sweden and no data has left Sweden, which is in accordance with Swedish law. The researchers had no access to names, personal numbers, or other personal identifiers in order to protect the integrity of all individuals included in the present study.

3. Results

Table 1 shows the characteristics of the study population. Among the 188,907 subjects, 22,014 unique cases with a first episode of depression were identified during the follow-up period. Of these, the majority (20,523 cases) was detected in primary healthcare settings. In total, 3,294 (1.7%) individuals had a family history of depression. Among the total study population at baseline, 57.6% were women.

Table 2 shows the results of the multilevel logistic regression models for men. Family history of depression was associated with significantly greater odds of depression (OR = 1.81, 95% CI = 1.52–2.16; *Model 1*). The OR for depression remained significant after adjustment for neighborhood social capital and neighborhood deprivation (*Model 2*). In *Model 3*, a similar pattern was observed as that in *Model 2*; after adding the individual and familial socioeconomic factors, the OR for depression remained significant (OR = 1.95, 95% CI = 1.66–2.29).

Table 3 shows the results of the cross-classified multilevel logistic regression models for women. As shown in men, family history of depression was associated with significantly greater odds of depression (OR = 1.58, 95% CI = 1.39–1.81; *Model 1*). The OR for depression remained significant after adjustment for neighborhood social capital and neighborhood deprivation (*Model 2*). In *Model 3*, a similar pattern was observed as that in *Model 2*. After adding the individual and familial socioeconomic factors, the OR for depression remained significant (OR = 1.66, 95% CI = 1.46–1.89).

There were no statistically significant interactions.

4. Discussion

To the best of our knowledge, this is the first large-scale follow-up study to examine the potential independent effect of family history of depression after adjustment for individual and familial socioeconomic factors (i.e., country of origin, educational attainment, family income and mobility) and neighborhood environmental factors (i.e., neighborhood deprivation and neighborhood social capital). Our results show that family history of depression increased the odds of depression in both men and women (OR = 1.95 in men and 1.66 in women), independent of individual, familial, and neighborhood factors.

A meta-analysis of family studies found that the offspring of depressed people are around three times more likely to experience major depression (Sullivan et al., 2000). Although the familial risks for depression in our study were lower than those in the above-mentioned study, our results also add evidence that supports the familial nature of depression. It is important to note that most of our cases were diagnosed in primary healthcare settings, which means that they were most likely less severe than people diagnosed with major depression in hospital settings. It is also possible that the three-fold increase in familial risk for major depression represented a larger genetic contribution than in our study, focusing mostly on depression diagnosed in primary healthcare settings.

A previous study indicated that the mechanisms underlying familial risk for depression could be genetic, individual, and environmental (Avenevoli and Merikangas, 2006). To provide clues regarding mechanisms, this study used cross-classified multilevel models that considered the effect of individual- and neighborhood-level factors simultaneously. Although our results could be influenced by other unmeasured risk factors for depression, the offspring of parents with depression are important targets for disease prevention, regardless of individual and familial socioeconomic factors and neighborhood environmental factors. A recent genome-wide study found that single nucleotide polymorphisms were associated with an increased risk for depression in a cohort of people of European descent (Hyde et al., 2016). Considering these results, it is not surprising that depression may constitute a familial disorder, and that its familiarity may mostly result from genetic influences (Sullivan et al., 2000).

In addition to family history of depression, our results support previous findings on the determinants of depression. For example, in our study, higher age, lower educational attainment, and lower family income were associated with depression in both men and

women. Higher neighborhood deprivation was also associated with depression. Considering these results, individuals with lower socio-economic status (SES) could be more exposed to psychosocial stress than higher SES individuals and may have less resources to cope with such stress (Lorant et al., 2003), which may cause an increased risk of depression. Similarly, people living in more deprived neighborhoods could be exposed to neighborhood stressors due to unsafe environments related to violent crime (Sundquist et al., 2006). These findings indicate that both individual- and neighborhood-level approaches are important in preventing depression.

It should also be noted that results could vary according to follow-up time. A recent meta-analysis found that there was a significant association between neighborhood socioeconomic conditions and depression in studies with less than 5 years of follow-up, but no association was found in studies with more than 5 years of follow-up (Richardson et al., 2015). One possible explanation for this is that individual-level characteristics could have varied with time, and that these characteristics could have influenced vulnerability to neighborhood conditions (Richardson et al., 2015). In this study, we accounted for mobility in order to partly remedy this.

The present study has several strengths. First, depression was identified from medical records, which means that the cases of depression were based on clinical examinations by physicians, and 22,014 cases with a first episode of depression were identified during the study period. Second, to the best of our knowledge, this is the first large-scale study to examine the longitudinal association between family history of depression and depression after adjustment for individual and familial socioeconomic factors (i.e., country of origin, educational attainment, family income and mobility), and environmental factors (i.e., neighborhood deprivation and neighborhood social capital). Finally, the prospective design of our study is stronger than a cross-sectional design, indicating potential effects of the exposure. However, the present study also had some limitations. First, our results could be explained by other unmeasured socioeconomic and environmental risk factors for depression. Second, we only studied one Scandinavian country; further studies in other countries are needed to determine whether the findings can be generalized to other cultural settings. Third, our measure of depression only included those individuals seeking treatment for depression; we had no access to data on the proportion of people with depression who did not seek treatment in Sweden during this time period. However, the universal health care in Sweden makes it quite possible that a higher proportion of cases received treatment in Sweden compared to many other countries, where only 51% of people with depression during the past 12 months in the U.S. had received treatment (Kessler et al., 2003). Given that Sweden has universal healthcare, our results may therefore be influenced to a lesser extent by those untreated depression cases than results from many other countries. However, it is possible that the generalizability of our findings is, at least to a certain extent, limited to those individuals who sought care for their depression. Another potential limitation in the diagnostic procedures is that the nationwide nature of our data implied that it was not possible to use a standardized instrument in all diagnostic procedures. In addition, parents with more severe depression may be more likely to be diagnosed with depression and their offspring may be more likely to develop depression. Fifth, the parents were past the median age of onset of depression at the beginning of the study period, which may have caused

misclassification of family history of depression. To minimize this bias, we did not exclude those parents with prevalent depression and limited the upper age of the offspring. Despite these limitations, we believe that the validity of our measure for depression is high because: it is likely that relatively few untreated cases were actually missed compared with many other studies, the study population was based on individuals from 20 years of age (minimizing the number of missing individuals with depression), prevalent cases of familial depression were not excluded, and the outcome measure was based on data from inpatient and outpatient specialist care in addition to primary health care and, finally, Swedish diagnostic procedures have, in general, a very high validity (Ludvigsson et al., 2011).

Although our results could be influenced by other unmeasured risk factors, the present study is a contribution to previous research that has shown that depression is heritable; the additional consideration of individual and familial socioeconomic factors and neighborhood environmental factors is something novel, indicating that familial risk of depression is independent of these individual, familial and neighborhood factors. The offspring of parents with depression are therefore important targets for disease prevention in clinical practice, at least in most industrialized countries.

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Highlight

- This 7-year follow-up study included 188,907 individuals aged 20–44 years.
- Familial history of depression is an independent risk factor for depression.
- Our results were adjusted by individual and familial SES, and neighborhood factors.
- Offspring of parents with depression are important targets for prevention.

Table 1

Characteristics of study population

	Study population		Depression cases	
	(*N*)	(%)	(*N*)	(%)
Total population	188,907		22,014	
Neighborhood-level factors				
Neighborhood deprivation				
Low	59,301	31.4	5,829	26.5
Moderate	79,916	42.3	9,419	42.8
High	49,690	26.3	6,766	30.7
Neighborhood social capital				
Low	64,661	34.2	8,332	37.8
Intermediate	89,245	47.2	10,324	46.9
High	35,001	18.5	3,358	15.3
Individual-level factors				
Sex				
Men	80,072	42.4	6,486	29.5
Women	108,835	57.6	155,28	70.5
Age (years)				
20–24	31,981	16.9	2,448	11.1
25–29	36,565	19.4	3,627	16.5
30–34	40,047	21.2	4,688	21.3
35–39	43,092	22.8	5,750	26.1
40–44	37,222	19.7	5,501	25.0
Country of origin				
Sweden	147,235	77.9	16,309	74.1
Finland	4,347	2.3	634	2.9
Western countries	1,395	0.7	136	0.6
Eastern European countries	2,667	1.4	424	1.9
Middle Eastern countries	15,084	8.0	2,448	11.1
Others	18,179	9.6	2,063	9.4
Educational attainment				
≤ 9 years	26,965	14.3	4,041	18.4
10–11 years	49,866	26.4	7,050	32.0
≥ 12 years	112,076	59.3	10,923	49.6
Family income				
Quartile 1 (Low income)	47,285	25.0	6,935	31.5
Quartile 2	47,195	25.0	6,340	28.8
Quartile 3	47,252	25.0	5,180	23.5
Quartile 4 (High income)	47,175	25.0	3,559	16.2
Mobility				
Not moved	99,276	52.6	12,474	56.7

	Study population		Depression cases	
	(*N*)	(%)	(*N*)	(%)
Moved	89,631	47.4	9,540	43.3
Depression				
Never depression	147,991	78.3		
Inpatient admission	1,269	0.7	570	2.6
Outpatient visit	2,251	1.2	921	4.2
Primary care visit	37,396	19.8	20,523	93.2
Family history of depression				
No	185,613	98.3	21,447	97.4
Yes	3,294	1.7	567	2.6

Table 2

Odds ratios (OR) and 95% credible intervals (CI) for depression in men; Results of cross-classified multi-level logistic regression models

	Model 1			Model 2			Model 3			
	OR	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**		**P-value**
Family history of depression (ref. No)	1.81	1.52	2.16	1.79	1.52	2.12	1.95	1.66	2.29	<0.001
Linking social capital (ref. High)										
Low				1.10	0.95	1.27	1.14	0.98	1.32	0.089
Intermediate				1.17	1.05	1.31	1.21	1.07	1.36	0.002
Neighborhood deprivation (ref. Low)										
Moderate				1.20	1.08	1.33	1.12	1.01	1.25	0.036
High				1.50	1.32	1.70	1.26	1.10	1.45	<0.001
Age							1.04	1.03	1.04	<0.001
Family income (ref. Highest quartiles)										
Middle-high income							1.34	1.24	1.45	<0.001
Middle-low income							1.32	1.22	1.44	<0.001
Low income							1.49	1.36	1.62	<0.001
Education attainment (ref. ≥ 12 years)										
≤ 9 years							1.46	1.36	1.58	<0.001
10–11 years							1.25	1.18	1.33	<0.001
Country of origin (ref. Sweden)										
Finland							1.08	0.90	1.30	0.424
Western countries							0.96	0.72	1.29	0.407
Eastern European countries							1.41	1.16	1.72	<0.001
Middle Eastern countries							1.24	1.12	1.38	<0.001
Others							0.92	0.84	1.02	0.110
Mobility (Moved vs. ref Not moved)							1.00	0.95	1.06	0.920
Neighborhood variance (S.E.)	*0.127 (0.018)*			*0.080 (0.012)*			*0.084 (0.013)*			
Family variance (S.E.)	*0.784 (0.074)*			*0.531 (0.057)*			*0.438 (0.056)*			
Intra class correlation in neighborhood	0.030			0.021			0.022			
Intra class correlation in family	0.187			0.136			0.115			

Table 3

Odds ratios (OR) and 95% credible intervals (CI) for depression in women; Results of cross-classified multi-level logistic regression models

	Model 1			Model 2			Model 3			
	OR	**95% CI**		**OR**	**95% CI**		**OR**	**95% CI**		**P-value**
Family history of depression (ref. No)	1.58	1.39	1.81	1.55	1.36	1.76	1.66	1.46	1.89	<0.001
Linking social capital (ref. High)										
Low				1.00	0.88	1.14	1.02	0.90	1.16	0.689
Intermediate				1.04	0.94	1.15	1.06	0.96	1.16	0.271
Neighborhood deprivation (ref. Low)										
Moderate				1.10	1.00	1.21	1.01	0.92	1.11	0.842
High				1.40	1.24	1.59	1.11	0.97	1.27	0.046
Age							1.04	1.03	1.04	<0.001
Family income (ref. Highest quartiles)										
Middle-high income							1.43	1.34	1.51	<0.001
Middle-low income							1.72	1.62	1.82	<0.001
Low income							1.80	1.69	1.92	<0.001
Maternal education attainment (ref. ≥ 12 years)										
≤ 9 years							1.60	1.51	1.68	<0.001
10–11 years							1.40	1.33	1.46	<0.001
Country of origin (ref. Sweden)										
Finland							1.04	0.93	1.17	0.424
Western countries							0.86	0.66	1.11	0.271
Eastern European countries							1.36	1.17	1.58	<0.001
Middle Eastern countries							1.46	1.35	1.58	<0.001
Others							0.89	0.83	0.96	0.001
Mobility (Moved vs. ref Not moved)							0.97	0.93	1.00	0.072
Neighborhood variance (S.E.)	*0.196 (0.019)*			*0.151 (0.016)*			*0.114(0.011)*			
Family variance (S.E.)	*0.838 (0.099)*			*0.508 (0.055)*			*0.486(0.058)*			
Intra class correlation in neighborhood	0.045			0.038			0.029			
Intra class correlation in family	0.194			0.129			0.125			