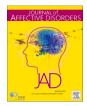
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The association between the social environment of childhood and adolescence and depression in young adulthood - A prospective cohort study

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ABSTRACT

Background: Good social relationships with parents and peers protect children and adolescents from developing mental disorders in adulthood while several negative experiences increase the risk of depression in later life. Methods: We used population-based cohort data from the Northern Finland Birth Cohort (NFBC) 1986. Participants (n=6147), their teachers and parents reported factors associated with the social environment of children and adolescents. Diagnoses of depression of cohort members were derived from Finnish nationwide registers. We conducted regression analyses to assess which factors of the social environment of childhood and adolescence were associated with depression in young adulthood.

Results: Bullying victimization in adolescence was the strongest predictor of depression in young adulthood among girls (OR 2.23: 95% CI 1.47–3.39) and boys (OR 2.44: 95% CI 1.49–4.00). Loneliness and bullying behavior in childhood were associated with depression in boys only. Loneliness in adolescence (OR 1.63: 95% CI 1.30–2.04) was associated with depression among both genders. Spending with the family seemed to protect against the negative impact of bullying and loneliness.

Limitations: We used single-item study questions to measure social relationships. These questions do not necessarily describe the phenomena as accurately as the measures validated for them.

Conclusion: Problems in social relationships with peers in childhood and adolescence are associated with depression in young adulthood. Time spent with the family is emphasized in situations in which adolescents have problems in peer-relationships.

1. Introduction

The social environment has a significant impact on the development of children and adolescents. In early childhood, the most important social reference group is the family, while the importance of peers clearly increases from middle childhood onwards. Social support from parents and peers plays a major role in an individual's life course (Malik and Marwaha, 2020). Good social relationships with parents and peers protect children and adolescents from developing mental disorders in adulthood (Orben et al., 2020; Steiner et al., 2019) while several negative experiences in childhood and adolescence increase the risk of

depression in later life (Kendler and Gardner, 2014).

Depression is a common mental disorder in different stages of life, but its highest prevalence is in young adulthood, with the average age of onset in the mid-20s (Kessler and Bromet, 2013). Depression is associated with increased morbidity and mortality and is one of the most debilitating mental disorder (GBD, 2018). Many of the risk factors for depression are related to social, structural and health issues in the childhood family. Parental attention and support are vital for children's development during their first years, but adolescents also need parental support in developing their mental resources (Malik and Marwaha, 2020). Family structure and problems in parenting practices have been

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associated with depression in previous studies. Parental divorce (Sands et al., 2017), single parent family (Laukkanen et al., 2016) and restructured family (Park and Lee, 2020) background have been associated with depression. Parenting practices such as low parental-warmth, more inter-parental conflict, over-involvement and aversiveness can be related to depression (Yap et al., 2014). Other family-related depression risk factors include low socioeconomic status (SES) of the family (Kessler and Bromet, 2013) and parental mental disorders (Leverton, 2003).

In a peer group, many of the immediate social and emotional needs of children and adolescents are met. Particularly during adolescence peers start to fulfill the needs that were previously fulfilled by parents. Adolescents start feeling a sense of belonging, intimacy and partnership with their peers. They receive feedback about themselves and use this feedback to build on their self-image (Coghill et al., 2009). When left alone outside their peer group, children and adolescents are at risk of failing to meet their social needs and this can affect their mental wellbeing and increase depressive symptoms (Stickley et al., 2016). Bullying victimization can be even more harmful than lack of friends or loneliness. At worst, bullying victimization can be a very traumatic experience and is a significant risk factor for depression in adulthood (McKay et al., 2021). Bullies themselves are also at risk of developing mental disorders later in life (Copeland et al., 2013). However, the relationship between problems in social relationships and depression is bidirectional. Although several studies demonstrate that depression is result of negative life-events, there is also evidence that temporal pattern begins with internalizing problems (Da Silva et al., 2020, Vaillancourt et al., 2013, Kochel et al., 2012).

The risk factors for depression related to the social environment of childhood and adolescence have been widely studied. Prospective studies of the association between bullying and depression have been conducted (Kwong et al., 2019; Moore et al., 2017), but only a few have examined the association between bullying in childhood or adolescence with depression diagnosed in adulthood (Lereya et al., 2015a; Lereya et al., 2015b). The association between childhood or adolescent loneliness and depression in adulthood has been studied in cross-sectional studies (Stickley et al., 2016; Beutel et al., 2017) and retrospectively (Jiang and Wang, 2020; Bruni et al., 2018), but prospective studies with follow-up from childhood to adulthood are rare (Xerxa et al., 2021). Social relationships with family and their association with depression, on the other hand, have been studied prospectively with follow-up from adolescence to adulthood (Chen and Harris, 2019; Pettit et al., 2011), but their data on psychiatric symptoms are based on self-reports. The protective effect of family and friends on depression has been studied, but less prospective research has been conducted that would take into account the effect of both family and peers (Gariépy et al., 2016).

Although the risk factors in this area have been widely studied, there is a lack of studies that consider multiple risk factors concerning the social environment of childhood and adolescence, follow-up from childhood to adulthood and which use the clinical diagnosis of depression as a main outcome measure. The aim of our study was to examine how factors related to the social environment of childhood and adolescence are associated with the onset of depression in young adulthood. We were also interested in whether good social relationships with the family could provide protection from negative impact of poor social relationships with the peers and vice versa. We examine these interactions through two research questions: 1. How are social relationships with the family associated with depression in young adulthood? 2. How are social factors related to peers, such as number of friends, bullying and loneliness, associated with depression in young adulthood? Our hypothesis is that social relationships with peers and family in childhood and adolescence are associated with depression in young adulthood.

2. Methods

2.1. Sample

The Northern Finland Birth Cohort (NFBC) 1986 is a large population-based cohort. The original study population comprised 9432 live-born children with an expected delivery date between 1 July 1985 and 30 June 1986 in two former northern provinces of Finland. The first follow-up was when the children were 7 to 8 years of age and at the time 99.0% (n=9357) of the cohort were alive. Separate questionnaires were sent to the parents and teachers of the cohort members of which 90.0% (n=8370) of the parents and 91.7% (n=8525) of the teachers responded to the questionnaire. The teachers' questionnaire included questions about children's behavior and parents were asked about their marital status, education, work and children's health (University of Oulu, 1986).

The second follow-up was conducted when the adolescents were 15 to 16 of age. At the time, 99.0% (n = 9340) of them were alive. Separate questionnaires were then sent to the adolescents and their parents. A total of 77.9% (n = 7182) of adolescents and 74.5% (n = 6966) of parents responded to the questionnaire. The adolescents' questionnaire concerned family structure, friends, school, health, living habits, hobbies and behavior. The parents' questionnaire included items on their marital and social status, education, work, health and living habits and their children's behavior, health and development (University of Oulu, 1986). In this study, we utilized data collected during the mother's pregnancy and when the participants were aged 7-8 and 15-16 years of age. The sample comprised all those cohort members who had not been diagnosed with depression before the age of 17 and who had participated in either of the follow-ups (See Fig. 1). The age was limited to 17 years onwards on the basis that we wanted to reliably distinguish potentially causal relationship between the risk factors in adolescence and the diagnosis of depression in young adulthood.

2.2. Measures

In order to evaluate the depression in the participants, we identified diagnoses of depression by using national registers: the Finnish Institute for Health and Welfare (care register for health care, inpatient treatments, specialized care outpatient treatments), Social Insurance Institution (reimbursable medicines until 2005) and Finnish Center for Pensions (disability pensions until 2016) registers. In other words, the registers cover a wide range of diagnoses made in both specialized and primary care. All the above services are available to all Finns. We included all diagnoses of depression (ICD10: F32–F33, F34.1, F38.10) from the time the participant turned 17 years of age until the end of 2019.

In this study we describe the social environment of childhood and adolescence through the social relationships with their peers and family. These phenomena were measured using individual questions derived from Rutter B (Rutter, 1967) and Youth Self-Report (YSR) (Achenbach, 1991) scales. Rutter B is 26-item scale, originally designed to evaluate a child's behavior in school. The validity of the Finnish Rutter B scale was found to be good (Kresanov et al., 1998). The YSR scale is a psychiatric assessment tool for evaluating the competencies and problems of 11–18-year-old adolescents. The validity of the YSR scale was found to be good (Achenbach and Rescorla, 2001). In addition to these scales, we used individual questions that had been supplemented to the original questionnaires used in the cohort.

2.3. Social relationships with peers at 7-8 years of age

Social relationships with peers are described through the teachers' experience of loneliness and bullying behavior of children. They were measured through individual single-item questions derived from the Rutter B scale. Loneliness was measured by asking the teachers to

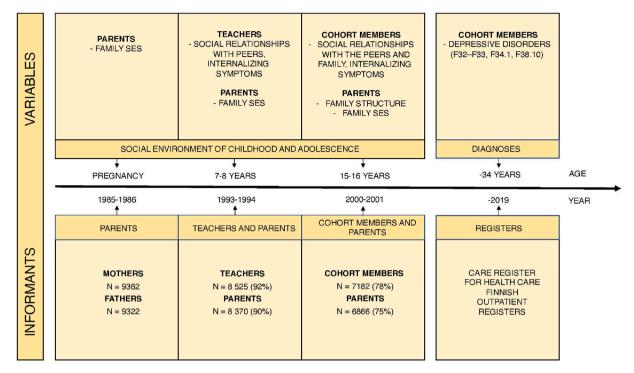


Fig. 1. Follow-up timepoints, informants and variables used in our study.

respond to the statement 'Has a tendency towards being alone, is quite seclusive' in the response options were: 'does not apply', 'applies somewhat' and 'certainly applies'. Bullying behavior was measured by asking the teachers to respond to the statement 'teases other children' and the response options were: 'does not apply', 'applies somewhat' and 'certainly applies'.

2.4. Social relationships with peers at 15-16 years of age

Adolescents were asked whether they had a close friend with whom they could talk in confidence about issues. The response options were: 'I have no close friends', 'I have one close friend', 'I have two close friends' and 'I have several close friends'. Loneliness was measured by asking the adolescents how well the statement 'I feel lonely' applied to them. The response options were: 'not true', 'somewhat or sometimes true' or 'very true or often true'. We derived this item from the YSR Scale, which was part of the adolescents' questionnaire. Bullying was measured by asking the adolescents to answer how well the statements 'I tease others a lot' and 'I get teased a lot' applied to them. The response options were: 'not true', 'somewhat or sometimes true' or 'very true or often true'. These questions were part of the YSR scale.

2.5. Social relationships with the family at 15-16 years of age

We collected the information on social relationships with the family by asking how often the adolescents spent time with their family: 'never', 'seldom', 'monthly', 'weekly' or 'daily' and whether their parents were interested in their school, hobbies and other things they considered important. The response options were: 'never', 'seldom' or 'nearly always'. Neither of these questions were part of the YSR scale but were added to the adolescents' original questionnaire by the researchers of the original cohort study.

2.6. Other variables

We used internalizing symptoms, family structure, family SES and parental psychiatric disorders as covariates. Internalizing symptoms in childhood were derived from the Rutter B2 scale and in adolescence from the YSR scale. Teachers' Rutter B2 scale includes four questions which are considered to measure internalizing symptoms (e.g., 'Is often worried' and 'Seems often low-spirited, unhappy, weepy or anguished'). YSR includes 30 items for internalizing symptoms (e.g., 'I am unhappy, sad or depressed' and 'I worry a lot'). We measured family structure by asking parents to select the alternatives that best described their marital status: 'married/cohabiting with the child's biological parent', 'divorced, single parent/coparent', 'divorced, re-married/cohabiting', 'single' or 'widow/widower'. In the analyses, family structure was categorized as 'nuclear family' and 'others'. We utilized the data collected when the participants were 15-16 years of age. We used parental level of education and employment status as markers of the family's socioeconomic status (SES). Education level was estimated by the highest level of education achieved by the parents by the time their child was 15-16 years of age. Information about employment status was collected from both parents during the mother's pregnancy. Employment status was categorized into professionals ('entrepreneurs', 'professionals' and other 'white collar workers') and non-professionals. We assessed the family's SES according to the highest employment status of either parent by the time of the second follow-up in 2000-2001. Parental level of education and employment status were combined as one SES variable and categorized into high and low SES. We obtained the information on the diagnoses of the parents (yes/no) from the National Institute for Health and Welfare register until 2019. We included all mental disorder diagnoses (ICD10: F00-F69, F80-F99) to the analyses.

2.7. Data analysis

We analyzed the data by statistical methods using SPSS Statistics (version 27.0, IBM Corporation). Internalizing symptoms were categorized using the 84th percentile by gender in Rutter B2 and YSR (Achenbach and Rescorla, 2001) as a cut-off for high and low internalizing symptoms. All other variables were categorical and were dichotomized for the multivariable analysis to clarify the results. All the variables are presented in Table 1. The results were considered statistically significant when the analysis resulted in a p-value of <0.05.

Table 1Background information and social environment of participants.

	Boys		Girls		Total	
	N	%	N	%	N (%)	
Parent's marital status at 15–16					5957	
years of age					(96.9)	
Married/cohabiting with the	2299	74.6	2294	74.8		
child's biological parent Divorced, single parent/	364	11.8	330	10.8		
coparent	304	11.0	330	10.6		
Divorced, re-married/cohabiting	214	6.9	249	8.1		
Single	27	0.9	41	1.3		
Widow	63	2.0	63	2.1		
Family SES					6147	
Higher	1725	56.0	1755	57.3	(100.0.)	
Lower	1354	43.9	1310	42.7	61.47	
Parental psychiatric disorders No	1946	63.1	1995	65.1	6147 (100.0)	
Yes	1136	36.9	1070	34.9	(100.0)	
Participant's diagnoses of	1100	50.5	10/0	01.5	6147	
depression after 17 years of age					(100.0)	
No	2867	93.0	2678	87.4		
Yes	215	7.0	387	12.6		
Participant's internalizing					6087	
symptoms at 7–8 years of age	0=0-	o	0===	oo -	(99.0)	
Low	2502	81.2	2552	83.3		
High Participant's internalizing	545	17.7	488	15.9	4940	
Participant's internalizing symptoms at 15–16 years of age					(80.4)	
Low	1971	64.0	2132	69.6	(00.7)	
High	413	13.4	424	13.8		
Social relationships with peers at 7–8	3 years of	f age				
Loneliness	0506	00.0	0500	04.4	6138	
Does not apply Applies somewhat	2536 454	82.3 14.7	2588 416	84.4 13.6	(99.9)	
Certainly applies	86	2.8	58	1.9		
Being a bully	00	2.0	50	1.,	6124	
Does not apply	2338	75.9	2843	92.8	(99.6)	
Applies somewhat	614	19.9	198	6.5		
Certainly applies	119	3.9	12	0.4		
Social relationships with peers at 15- Close friends	-16 years	of age			E602	
No close friends	288	9.3	93	3.0	5692 (92.6)	
One close friend	744	24.1	590	19.2	(92.0)	
Two close friends	501	16.3	812	26.5		
Several close friends	1221	39.6	1443	47.1		
Loneliness					5715	
	0051	50.0	1784	58.2	(93.0)	
Not true	2251	73.0	1/04		(50.0)	
Somewhat or sometimes true	475	15.4	1028	33.5	(30.0)	
Somewhat or sometimes true Very true or often true				33.5 3.8		
Somewhat or sometimes true Very true or often true Being a bully	475 60	15.4 1.9	1028 117	3.8	5709	
Somewhat or sometimes true Very true or often true Being a bully Not true	475 60 2055	15.4 1.9 66.7	1028 117 2403	3.8 78.4		
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true	475 60 2055 707	15.4 1.9 66.7 22.9	1028 117 2403 509	3.8 78.4 16.6	5709	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true	475 60 2055	15.4 1.9 66.7	1028 117 2403	3.8 78.4	5709 (92.9)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true	475 60 2055 707	15.4 1.9 66.7 22.9	1028 117 2403 509	3.8 78.4 16.6	5709	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization	475 60 2055 707 23	15.4 1.9 66.7 22.9 0.7	1028 117 2403 509 18	3.8 78.4 16.6 0.6	5709 (92.9)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true	475 60 2055 707 23 2616	15.4 1.9 66.7 22.9 0.7 84.9	1028 117 2403 509 18 2787	3.8 78.4 16.6 0.6 90.9	5709 (92.9)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true	475 60 2055 707 23 2616 147	15.4 1.9 66.7 22.9 0.7 84.9 4.8	1028 117 2403 509 18 2787 126	3.8 78.4 16.6 0.6 90.9 4.1	5709 (92.9)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Social relationships with the family a	475 60 2055 707 23 2616 147 13	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4	1028 117 2403 509 18 2787 126 17	3.8 78.4 16.6 0.6 90.9 4.1	5709 (92.9) 5706 (92.8)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Somewhat or sometimes true Very true or often true	475 60 2055 707 23 2616 147 13	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4	1028 117 2403 509 18 2787 126 17	3.8 78.4 16.6 0.6 90.9 4.1	5709 (92.9) 5706 (92.8)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Somewhat or sometimes true Very true or often true Social relationships with the family a Parents interest towards their adolescent's issues	475 60 2055 707 23 2616 147 13	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4	1028 117 2403 509 18 2787 126 17	3.8 78.4 16.6 0.6 90.9 4.1 0.6	5709 (92.9) 5706 (92.8)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Somewhat or sometimes true Very true or often true Social relationships with the family a Parents interest towards their adolescent's issues Never	475 60 2055 707 23 2616 147 13 at 15–16	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4 years of	1028 117 2403 509 18 2787 126 17	3.8 78.4 16.6 0.6 90.9 4.1 0.6	5709 (92.9) 5706 (92.8)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Somewhat or sometimes true Very true or often true Social relationships with the family a Parents interest towards their adolescent's issues Never Seldom	475 60 2055 707 23 2616 147 13 at 15–16	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4 years of	1028 117 2403 509 18 2787 126 17 age	3.8 78.4 16.6 0.6 90.9 4.1 0.6	5709 (92.9) 5706 (92.8)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Somewhat or sometimes true Very true or often true Social relationships with the family a Parents interest towards their adolescent's issues Never	475 60 2055 707 23 2616 147 13 at 15–16	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4 years of	1028 117 2403 509 18 2787 126 17	3.8 78.4 16.6 0.6 90.9 4.1 0.6	5709 (92.9) 5706 (92.8)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Somewhat or sometimes true Very true or often true Social relationships with the family a Parents interest towards their adolescent's issues Never Seldom Nearly always	475 60 2055 707 23 2616 147 13 at 15–16	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4 years of	1028 117 2403 509 18 2787 126 17 age	3.8 78.4 16.6 0.6 90.9 4.1 0.6	5709 (92.9) 5706 (92.8) 5716 (93.0)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Social relationships with the family a Parents interest towards their adolescent's issues Never Seldom Nearly always Spending time with the family	475 60 2055 707 23 2616 147 13 at 15–16	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4 years of 0.4 12.4 77.6	1028 117 2403 509 18 2787 126 17 age	3.8 78.4 16.6 0.6 90.9 4.1 0.6	5709 (92.9) 5706 (92.8) 5716 (93.0)	
Somewhat or sometimes true Very true or often true Being a bully Not true Somewhat or sometimes true Very true or often true Bullying victimization Not true Somewhat or sometimes true Very true or often true Somewhat or sometimes true Very true or often true Social relationships with the family a Parents interest towards their adolescent's issues Never Seldom Nearly always Spending time with the family Never	475 60 2055 707 23 2616 147 13 at 15–16 13 382 2391 50	15.4 1.9 66.7 22.9 0.7 84.9 4.8 0.4 years of 0.4 12.4 77.6	1028 117 2403 509 18 2787 126 17 age	3.8 78.4 16.6 0.6 90.9 4.1 0.6 0.6 12.3 82.7 0.9	5709 (92.9) 5706 (92.8) 5716 (93.0)	

N number

Missing data varied between 0.0 and 19.6%.

We used the logistic regression analyses to assess which factors of the social environment of childhood and adolescence (number of friends, loneliness, bullying, time spent with the family, parent's interest in their child's issues) were associated with depression in young adulthood. We performed the logistic regression analyses in overall sample and with both genders. Because there were gender differences in the results, we present the results by gender. Gender being statistically significant covariant in every model, we performed interaction analyses to see if gender interacts with social relationship variables. In additional analyses, we performed logistic regression to detect whether positive factors in social relationships with family (e.g., spending regular time with the family) could offer protection against the effect of loneliness or bullying. On the other hand, we wanted to see whether effects of friends could protect from the harmful effect of negative factors in social relationships with the family (e.g., rarely spending time with the family). We present the unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for associations.

We used internalizing symptoms, family structure, family SES and parental mental disorders as covariates when predicting the diagnoses of depression in young adulthood. We present the results of regression analyses with internalizing symptoms in childhood (7–8 years of age) as covariate, but also with adolescents' (15–16 years of age) internalizing symptoms as covariate (see Supplementary Table 1). The selection of the included covariates was based on the literature described above. The covariates that are associated with depression in young adulthood are presented.

2.8. Attrition analyses

According to the previous attrition analysis made for the NFBC data, boys participated less frequently than girls in the follow-up study, same as participants living in urban areas. Also, fewer adolescents with a parental history of psychiatric disorder participated than others (Miettunen et al., 2014).

3. Results

3.1. The sample

The final sample comprised 6147 participants (3065 girls and 3082 boys). Overall, 9,8% (n = 602) of cohort members had been diagnosed with depression by the end of 2019 and more than one third (35.9%) of the participants' parents had been diagnosed with a psychiatric disorder. Measured at 7-8 years of age boys reported more high internalizing symptoms than girls (17.7% vs 15.9%). By the time of adolescence high internalizing symptoms were experienced by 13.8% of girls and 13.4% of boys. Most of the adolescents lived in a nuclear family, while around 25% of them had some other family structure. Descriptive statistics of the social environment of children and adolescents are shown in Table 1. Among those adolescents whose parents did not cohabit, 9% of boys developed depression, compared with 18.4% of girls. In nuclear families the corresponding proportions were 6,4% of boys and 10.7% of girls. A slight majority of the cohort members belonged to the higher SES category (56.6%). Among boys, depression occurred in those members in the higher SES category among 7.4% and in the lower category among 6.5%. In girls, 12.6% had been diagnosed with depression in the higher SES category and 12.6% in the lower category. In this sample the prevalence of depression in young adulthood was significantly higher in girls compared to boys (unadjusted OR 1.90; 95% CI 1.59-2.27). All other background variables were also associated with depression in young adulthood in unadjusted models, with the except of family SES. These results are presented in Table 2. In interaction analyses the gender was not statistically significantly associated with variables of social environment (see Supplementary Table 1).

 $\begin{tabular}{ll} \textbf{Table 2} \\ \textbf{The association between background information and depression in young adulthood.} \\ \end{tabular}$

Depression diagnoses		
Parent's marital status at 15–16 years of age Nuclear family 6.4 Ref. 10.7 Ref. Other 9.0 1.45 18.4 1.89 (1.06–1.99) (1.50–2.39 Family SES Higher 7.4 Ref. 12.6 Ref. Lower 6.5 0.88 12.6 0.99 (0.66–1.16) (0.80–1.23) Parental psychiatric disorders No 5.3 Ref. 11.1 Ref. Yes 9.9 1.96 15.4 1.46 (1.48–2.59) (1.17–1.81	_	
status at 15–16 years of age Nuclear family 6.4 Ref. 10.7 Ref. Other 9.0 1.45 18.4 1.89 (1.06–1.99) (1.50–2.39 Family SES Higher 7.4 Ref. 12.6 Ref. Lower 6.5 0.88 12.6 0.99 (0.66–1.16) (0.80–1.23) Parental psychiatric disorders No 5.3 Ref. 11.1 Ref. Yes 9.9 1.96 15.4 1.46 (1.48–2.59) (1.17–1.81	OR (95% CI)	
years of age Nuclear family 6.4 Ref. 10.7 Ref. Other 9.0 1.45 18.4 1.89 (1.06–1.99) (1.50–2.39 Family SES Higher 7.4 Ref. 12.6 Ref. Lower 6.5 0.88 12.6 0.99 (0.66–1.16) (0.80–1.23) Parental psychiatric disorders No 5.3 Ref. 11.1 Ref. Yes 9.9 1.96 15.4 1.46 (1.48–2.59) (1.17–1.81		
Nuclear family 6.4 Ref. 10.7 Ref. Other 9.0 1.45 18.4 1.89 (1.06–1.99) (1.50–2.39 Family SES Higher 7.4 Ref. 12.6 Ref. Lower 6.5 0.88 12.6 0.99 (0.66–1.16) (0.80–1.23) Parental psychiatric disorders No 5.3 Ref. 11.1 Ref. Yes 9.9 1.96 15.4 1.46 (1.48–2.59) (1.17–1.81		
Other 9.0 1.45 18.4 1.89 (1.50–2.39) Family SES Higher 7.4 Ref. 12.6 Ref. Lower 6.5 0.88 12.6 0.99 (0.66–1.16) (0.80–1.23) Parental psychiatric disorders No 5.3 Ref. 11.1 Ref. Yes 9.9 1.96 15.4 1.46 (1.48–2.59) (1.17–1.81)		
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disorders No 5.3 Ref. 11.1 Ref. Yes 9.9 1.96 15.4 1.46 (1.48–2.59) (1.17–1.81		
No 5.3 Ref. 11.1 Ref. Yes 9.9 1.96 15.4 1.46 (1.48-2.59) (1.17-1.81		
Yes 9.9 1.96 15.4 1.46 (1.48-2.59) (1.17-1.81		
(1.48–2.59) (1.17–1.81		
Participant's)	
internalizing		
symptoms at		
7–8 years		
of age		
Low 7.0 Ref. 11.9 Ref.		
High 7.2 1.03 17.0 1.52		
(0.72–1.48) (1.17–1.98)	
Participant's		
internalizing		
symptoms at		
15–16 years of		
age		
Low 5.7 Ref. 10.2 Ref.		
High 12.8 2.44 21.5 2.41		
(1.73–3.45) (1.84–3.16)	

Significant associations shown in bold. *OR* odds ratio, *CI* confidence interval.

3.2. Social relationships with peers at 7-8 years of age

In childhood, loneliness was reported on some degree by 16.5% of participants. Loneliness was a risk factor for depression in young adulthood among boys (OR 2.08; 95% CI 1.47–2.95). In girls, there was no association (OR 1.07; 95% CI 0.79–1.45). Bullying behavior was reported in 15.3% of participants. If the cohort member had bullying behavior, it increased the risk of depression in boys (OR 1.75; 95% CI 1.29–2.39). No similar association was found among girls. See Table 3 for further details.

3.3. Social relationships with peers at 15-16 years of age

Most of the cohort members had at least one friend in adolescence. Around 6% of participants reported not having a close friend. Among boys, the absence of friends was associated with depression in young adulthood. The difference compared to those participants who had at least one friend was statistically significant OR 1.65 (95% CI 1.08–2.53). No similar difference was found in girls. Experiencing loneliness increased since the age of 7–8 years, meaning that over one third (37.3%) of the girls experienced loneliness on some degree at 15–16 years of age. Correspondingly, 17.3% of boys experienced loneliness on some degree. Loneliness appears to be a risk factor for depression among both genders (girls OR 1.96; 95% CI 1.56–2.47 and boys OR 1.79; 95% CI 1.27–2.52). When looking at the change that occurred during the follow-up, it can be noted that the impact of loneliness increased as it continued from childhood into adolescence. If loneliness was experienced since childhood, the risk of depression increased at 15–16 years of

age compared to those participants who did not experience loneliness.

By the time of adolescence 23.6% of boys and 17.3% of girls reported that they bullied others. The bullying behavior in adolescence was not associated with depression in young adulthood, except when the boy had been bullying others at both timepoints: at 7–8 and 15–16 years of age (OR 2.58; 95% CI 1.58–4.23). Around 5% of adolescents had experienced bullying victimization. Of all risk factors, bullying victimization was the strongest predictor of depression in young adulthood among girls (OR 2.23: 95% CI 1.47–3.39) and boys (OR 2.44: 95% CI 1.49–4.00).

3.4. Social relationships with the family at 15-16 years of age

For most adolescents, parents were interested in their adolescent's issues and regularly spent time with them. However, among 15–16-year-old boys, a statistically significant (p=0.001) proportion never (1.6%) spent time with their family compared to girls (0.9%). Parents' interest in their adolescent's issues was not statistically significantly associated with depression in young adulthood. However, not spending time with the family was associated with depression among boys in young adulthood. If a boy did not spend time with his family or the time spent was very random, the risk of depression significantly increased OR 1.76 (95% CI 1.27–2.44).

3.5. Covariates

From the covariates internalizing symptoms, parental psychiatric disorders, family structure and family SES were statistically significantly associated with depression (see Table 4). Internalizing symptoms in childhood were associated with depression in young adulthood among girls only. However, when we used internalizing symptoms in adolescence as covariate (see Supplementary Table 2), they were statistically significantly associated with depression in all models among both genders (data available from the authors). Among girls, other family structure than nuclear family was also associated with depression in young adulthood. Among boys, parental psychiatric disorders were associated with depression in young adulthood. Also, in one model high family SES was associated with depression among boys.

3.6. Additional analyses of protective factors

Spending time with the family appeared to be a protective factor in the additional analyses. The harmful impact of bullying was reduced among those adolescents who regularly spent time with their family. If a girl was bullied and did not spend regular time with the family, the risk of depression was clearly higher (OR 3.26; 95% CI 1.61–6.58), compared to an adolescent who spent time with the family (OR 2.00; 95% CI 1.20–3.35). In the case of loneliness, the results were similar. If the adolescent was experiencing loneliness, spending time with the family reduced the risk of depression. Having friends, on the other hand, was not as significant protective factor as spending time with the family. Having friends reduced the risk of depression in boys who did not spent time with their family (OR 1.83; 95% CI 1.28–2.61), compared to an adolescent who did not spent time with his family and had no friends (OR 2.01; 95% CI 1.01–4.02). The same beneficial impact was not found in girls. These results are presented in Table 5.

4. Discussion

4.1. Main results

Our results demonstrate that negative factors in childhood and adolescent social relationships with the family and peers are associated with depression in young adulthood. In particular, bullying victimization and loneliness can increase the risk of depression in young adulthood. This study also highlights the importance of spending time with

Table 3

The association between the social environment of childhood and adolescence and depression in young adulthood.

	Boys			Girls			
	Depression diagnoses	Unadjusted model	Adjusted model	Depression diagnoses	Unadjusted model	Adjusted model	
	%	OR (95% CI)	OR (95% CI)	%	OR (95% CI)	OR (95% CI)	
Social relationships with peers at	7–8 years of age						
Loneliness	-						
No	6.0	Ref.	Ref.	12.3	Ref.	Ref.	
Yes	11.1	1.95 (1.42-2.67)	2.08 (1.47-2.95)	14.3	1.20 (0.90-1.59)	1.07 (0.79-1.45)	
Being a bully							
No	6.0	Ref.	Ref.	12.3	Ref.	Ref.	
Yes	10.0	1.72 (1.28–2.32)	1.75 (1.29–2.39)	16.7	1.42 (0.97–2.08)	1.26 (0.85–1.88)	
Social relationships with peers at	15–16 years of age						
Close friends	, ,						
Yes	6.5	Ref.	Ref.	12.1	Ref.	Ref.	
No	10.1	1.60 (1.06-2.43)	1.65 (1.08-2.53)	17.2	1.51 (0.87-2.61)	1.54 (0.87-2.73)	
Loneliness							
No	6.0	Ref.	Ref.	9.2	Ref.	Ref.	
Yes	10.1	1.75 (1.26-2.43)	1.79 (1.27-2.52)	16.9	2.00 (1.60-2.50)	1.96 (1.56-2.47)	
Being a bully							
No	6.4	Ref.	Ref.	12.1	Ref.	Ref.	
Yes	8.1	1.28 (0.93-1.76)	1.32 (0.95-1.84)	12.5	1.04 (0.78-1.39)	1.02 (0.76-1.36)	
Bullying victimization							
No	6.5	Ref.	Ref.	11.6	Ref.	Ref.	
Yes	13.8	2.29 (1.43–3.69)	2.44 (1.49–4.00)	24.5	2.48 (1.67–3.70)	2.23 (1.47-3.39)	
Social relationships with the fami	ily at 15–16 years of age						
Family's interest							
Yes	6.6	Ref.	Ref.	11.8	Ref.	Ref.	
No	8.1	1.25 (0.84-1.85)	1.24 (0.83-1.87)	15.4	1.37 (1.01-1.84)	1.30 (0.96-1.77)	
Spending time with the family							
At least once a week	5.9	Ref.	Ref.	11.6	Ref.	Ref.	
Not at all/rarely	9.8	1.74 (1.26–2.39)	1.76 (1.27–2.44)	14.6	1.31 (1.00–1.70)	1.27 (0.97–1.66)	
Social relationships with peers, cl	hanges in time						
Loneliness							
No 7-8 years - no 15-16 years		Ref.	Ref.		Ref.	Ref.	
Yes 7-8 years - no 15-16 years	3	1.93 (1.28-2.89)	2.15 (1.40-3.33)		0.85 (0.52-1.40)	0.79 (0.47-1.32)	
No 7-8 years - yes 15-16 years	s	1.80 (1.21-2.67)	1.88 (1.25-2.81)		1.89 (1.48-2.41)	1.88 (1.46-2.42)	
Yes 7–8 years – yes 15–16 year	rs .	2.73 (1.57-4.72)	3.11 (1.72-5.64)		2.36 (1.61-3.46)	2.04 (1.36-3.07)	
Being a bully							
No 7–8 years – no 15–16 years		Ref.	Ref.		Ref.	Ref.	
Yes 7–8 years – no 15–16 years	3	1.44 (0.98-2.14)	1.50 (0.99-2.26)		1.40 (0.89-2.20)	1.27 (0.79-2.06)	
No 7-8 years - yes 15-16 years	s	1.09 (0.73-1.63)	1.11 (0.73–1.68)		1.05 (0.78-1.42)	1.03 (0.75–1.40)	
Yes 7–8 years – yes 15–16 year	rs	2.39 (1.48-3.85)	2.58 (1.58-4.23)		1.30 (0.58-2.94)	1.09 (0.48-2.49)	

Significant associations shown in bold.

All analyses adjusted for internalizing symptoms (at age of 7–8), family SES, family structure and parental psychiatric disorders. *OR* odds ratio, *CI* confidence interval.

the family. Regular time spent with the family was a protective factor in this sample, reducing the risk of depression, particularly in those participants who experienced loneliness or who were bullied by their peers.

4.2. Social relationships with peers as a risk factor for depression

Childhood loneliness was associated with depression in young adulthood only among boys. According to teachers, boys also experienced more loneliness in childhood than girls. By the time of adolescence, the number of girls experiencing loneliness had increased significantly and the association between loneliness and depression was found in both genders. Previous literature has produced mixed results concerning gender differences in experiencing loneliness in childhood and adolescence (Qualter et al., 2015), but the most recent meta-analysis (Maes et al., 2019) is in line with our result in that number of boys experiencing loneliness exceeds the number of girls experiencing loneliness in childhood. There has been a lack of studies concerning the association between childhood loneliness and depression in young adulthood resulting also in a knowledge gap in gender differences in this topic. One recent prospective study (Xerxa et al., 2021) assessed the

association between childhood loneliness and psychiatric disorders in adulthood and found association between childhood loneliness and depression symptoms in adulthood, but they did not report results by gender.

The topic of loneliness in adolescence has interested many researchers as adolescents are going through a fragile period when they experience social changes causing them a risk of loneliness (Qualter et al., 2015). In adolescence loneliness is found to be more strongly associated with depression among girls (Liu et al., 2020; Beutel et al., 2017; Matthews et al., 2016). It is suggested that compared to boys, girls might be more sensitive at the social context preferring to be more socially connected with others (Yang and Girgus, 2019; Cross and Madson, 1997) and base their self-esteem on the quality of their interpersonal relationships, including peers (Cambron et al., 2009). This might make girls more sensitive to the negative impact of loneliness. On the other hand, loneliness self-reports are shown to produce data, where loneliness is more common in girls than in boys (Borys and Perlman, 1985). Nevertheless, self-ratings are probably the best indicators of internal traits (Vazire, 2010) such as loneliness.

To our knowledge, this is the first study to assess the association

Table 4Significant covariates of logistic regression analyses.

	Boys	Girls		
	OR (95% CI)	OR (95% CI)		
Loneliness (7–8 years)	Parental psychiatric	Family structure 1.82		
	disorders 2.03	(1.43-2.32)		
	(1.51-2.72)	Internalizing symptoms		
		1.46 (1.09-1.95)		
Being a bully (7-8 years)	Parental psychiatric	Family structure 1.80		
	disorders 2.07	(1.41-2.29)		
	(1.55-2.77)	Internalizing symptoms		
		1.49 (1.13–1.95)		
Close friends (15-16	Parental psychiatric	Family structure 1.81		
years)	disorders 2.04	(1.41–2.32)		
•	(1.50-2.77)	Internalizing symptoms		
	Family SES 0.71	1.50 (1.14–1.99)		
	(0.52–0.97)			
Loneliness (15-16 years)	Parental psychiatric	Family structure 1.73		
	disorders 2.14	(1.34–2.23)		
	(1.57-2.92)	Internalizing		
		symptoms1.43		
		(1.08–1.90)		
Being a bully (15–16	Parental psychiatric	Family structure 1.71		
years)	disorders 2.13	(1.33–2.00)		
•	(1.56-2.89)	Internalizing symptoms		
		1.46 (1.10–1.94)		
Bullying victimization	Parental psychiatric	Family structure 1.71		
(15–16 years)	disorders 2.12	(1.33–2.20)		
	(1.55-2.88)	Internalizing symptoms		
	· ·	1.41 (1.06–1.88)		
Family's interest (15-16	Parental psychiatric	Family structure 1.79		
years)	disorders 2.07	(1.40–2.30)		
,	(1.52-2.82)	Internalizing symptoms		
	, ,	1.48 (1.11–1.97)		
Spending time with the	Parental psychiatric	Family structure 1.75		
family (15–16 years)	disorders 2.13	(1.36–2.26)		
, (- ·) - · - ·	(1.56–2.91)	Internalizing symptoms		
	,	1.50 (1.14–1.99)		

Table 5The association between social relationships with the family and peers.

	Boys	Girls
	Adjusted OR (95% CI)	Adjusted OR (95% CI)
Loneliness (yes/no) – spending time with		
the family (yes/no)		
No – yes	Ref.	Ref.
No – no	1.70	1.26 (0.84-1.88)
	(1.15-2.52)	
Yes – yes	1.79	1.94
	(1.17-2.75)	(1.49-2.53)
Yes – no	2.93	2.37
	(1.73-4.96)	(1.63-3.44)
Bullying victimization (yes/no) - spending		
time with the family (yes/no)		
No – yes	Ref.	Ref.
No – no	1.83	1.17 (0.87-1.56)
	(1.29-2.59)	
Yes – yes	2.81	2.00
	(1.54-5.14)	(1.20-3.35)
Yes - no	3.28	3.26
	(1.42-7.61)	(1.61-6.58)
Spending time with the family (yes/no) - friends (yes/no)		
Yes – yes	Ref.	Ref.
Yes – no	1.79 (1.02–3.11)	1.48 (0.76–2.85)
No – yes	1.83	1.27 (0.96–1.67)
140 – yes	(1.28–2.61)	1.2/ (0.50-1.0/)
No – no	2.01 (1.01–4.02)	2.38 (0.76–7.40)

Significant associations shown in bold.

All analyses adjusted for internalizing symptoms (at age of 7–8), family SES, family structure and parental psychiatric disorders. *OR* odds ratio, *CI* confidence interval.

between childhood loneliness and depression in young adulthood that found differences between genders. The gender differences in the association between loneliness and depression in young adulthood were found in childhood but ceased to be significant by the time the child reached adolescence. One possible explanation is the fact that childhood loneliness was assessed by teachers and adolescents' loneliness was assessed by self-reports. As loneliness is subjectively experienced emotion, and it can be difficult for teachers to reliably assess (Galanaki and Vassilopoulou, 2007). Of course, it is also possible that boys are more vulnerable for depression when experiencing loneliness in childhood. It is unclear which mechanisms underlie the gender differences, but the evolutionary theory of loneliness suggest that loneliness can contribute for example to increased vigilance for social threats, increased anxiety, hostility, social withdrawal and increased sleep fragmentation, which all may increase the risk of depression (Cacioppo et al., 2014). In future research in this area, researchers should focus on examining the gender differences in childhood loneliness and its association with depression in adulthood.

In our study, bullying experienced in adolescence was the strongest risk factor for depression in young adulthood. This result is consistent with previous knowledge in this area field (McKay et al., 2021; Moore et al., 2017). Bullying affects a person's self-esteem and future optimism. It causes toxic stress that negatively affects behavioral and mental health (Evans et al., 2018). An alternative explanation is that internalizing symptoms preceded the victimization. Adolescents who are experiencing internalizing symptoms can be seen as easy targets for victimization by bullies (Fekkes et al., 2006). A bully has also found to be at risk of mental illness (Sourander et al., 2007). In our study, according to the teacher's assessment in childhood and self-reports in adolescence, boys bullied others more than girls. The gender differences were clearly obvious in childhood than in adolescence. Association between bullying behavior and depression were also found in boys only. One possible explanation for the gender differences is that male bullies were also victims of bullying. According to (Luukkonen et al., 2010) as bully victims boys may be more vulnerable for depression than girls. In our study we were not able to confirm if the bullies were also bully victims in both timepoints, but the association with depression and bully victimization was stronger in boys than girls. Other possible explanation is that teachers might have evaluated boys more negatively than girls (Mullola et al., 2012). Gender differences in depression and bully victimization needs further studies.

4.3. Social relationships with the family as a risk and protective factor for depression

According to our results, social relationships with the family can act as both a protective and a risk factor for depression. Among boys, the risk of depression significantly increased in those adolescents who did not regularly spend time with their family, or the time spent together was very random. Among all adolescents, spending time with the family was a protective factor for those in risk of depression caused by peer-related factors. Also, based on the previous literature, positive family relationships can protect against depression (Chen and Harris, 2019; Gariépy et al., 2016). Parental support has been found to be particularly important for girls (Gariépy et al., 2016) In our sample on those adolescents who were at risk of depression due to bullying victimization, time spent with their family was particularly important for girls. The risk of depression due to loneliness, however, decreased more in boys than girls when an adolescent was regularly spending time with their family.

4.4. Covariates as a risk factor for depression

Consistent with the previous knowledge, gender was associated with depression in young adulthood. Women typically have a two-fold increased risk of major depression compared to men (Kessler and Bromet, 2013; van de Velde et al., 2010). The adolescent family structure

was associated with depression in young adulthood among girls. This result is consistent with the previous literature, which has demonstrated the association between depression and different family structures other than the nuclear family (Park and Lee, 2020; Sands et al., 2017; Laukkanen et al., 2016; Bakker et al., 2012). However, it is important to understand that family structure itself does not cause depression, but factors related to changes in family structure can affect the mental wellbeing of children and adolescents. For example, the loss of a parent due to serious illness, death or divorce is a risk factor for depression (Simbi et al., 2020). If a child's immediate environment is not able to help it deal with the loss of a parent in such situations, the loss may increase the risk of subsequent depressive conditions (Wasserman, 2011).

High family SES was associated with depression in young adulthood among boys in our sample. Other studies have demonstrated the connection between lower SES and depression (Lorant et al., 2003). In our study, family SES was measured using parental level of education and employment status, although parental income was not considered. Andrade et al. (2003) found that income level is a more sensitive measure for detecting the association with depression than educational level. However, another Finnish study using the same SES variables that we used, found that depression almost doubled among those adolescents whose parents were unemployed and had a low level of education (Torikka et al., 2014), the difference being that this other study used the self-reported depressive symptoms of adolescents, while our study examined the morbidity of young adults based on nationwide register data.

In our sample parental psychiatric disorders were associated with depression of boys in young adulthood. The intergeneration of depression is a well-known fact based on the previous literature (van Santvoort et al., 2015). However, the intergenerational transmission of mental health issues is a complex phenomenon that includes both biological and environmental aspects. The genome is proposed to explain around 30-40% of the risk of developing depression in adulthood (Nivard et al., 2015), but parental psychiatric disorders also affect the mental development of children through parenting practices and the child's socioemotional needs. For example, mother's depression is associated with more hostile, negative parenting, more withdrawn and less positive parenting (England and Sim, 2009). However, it should be noted that depression is not only an individual and family illness, but also has its roots in the social environment at large. In an individualizing society, in which mental disorders continue to be stigmatized, a sense of community disappears, social support decreases and individual responsibility and stress increases (Rössler, 2016). The causes of depression do not always disappear or diminish simply by helping and caring for an individual and their family, but the elimination of depression would often require social and cultural changes.

4.5. Strengths and limitations

The main strength of this study is its longitudinal study design. With a prospective cohort study, we were trying to assess causality of childhood and adolescence social environment and depression in young adulthood. Even though there is a possibility that problems in mental health preceded the depression, we were able to control the effects of several factors, including internalizing symptoms. Main results remained statistically significant after controlling the effect of internalizing symptoms and it improves the reliability of the results. The sample was representative of the target population from a large area of Northern Finland. The population of Northern Finland is quite homogeneous, and ethnicity does not play a major role in the area. That is why the sample lacks generalizability to heterogeneous regions. We were able to use nationwide registers to collect the diagnosed mental disorders of cohort members and their parents. Using the nationwide registers, risk factors for mental disorders can be reliably identified. Registries provide data where the risk of bias is minimal (Miettunen et al., 2011). Not all people with depression seek treatment, but health

care is available to everyone in Finland. The registers show extensive information on both specialist care and primary health care. Only occupational health information does not appear in these registers. The data we utilized, were only collected at two timepoints and we were not able to fully study the same phenomena at both timepoints. Also, we used single-item study questions to measure social relationships. These questions do not necessarily describe the phenomena as accurately as the measures validated for them. For loneliness, the single-item selfreport is a valid and widely used measure, particularly in large surveys (Moisio and Rämö, 2007). However, it is recommended that bullying, for example, is measured using scales that have been validated to measure a range of bullying experiences (Hamburger et al., 2011). It should also be noted that in our study, social relationships with the family have been described in terms of how much time adolescents spend with their family and whether the family is interested in their adolescent's issues. These do not necessarily reflect the amount or quality of support provided by the family and therefore previous studies are not completely comparable.

5. Conclusion

According to our findings, problems in social relationships with peers in childhood and adolescence are associated with depression in young adulthood. Especially, bullying victimization and loneliness can increase the risk of depression in young adulthood. Time spent with the family is emphasized in situations in which adolescents have problems in peer-relationships. Our findings can have important implications for the implementation of interventions targeted to the risk factors of depression.

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Availability of data and material

NFBC data is available from the University of Oulu, Infrastructure for Population Studies. Permission to use the data can be applied for research purposes via electronic material request portal. In the use of data, we follow the EU general data protection regulation (679/2016) and Finnish Data Protection Act. The use of personal data is based on cohort participant's written informed consent at his/her latest follow-up study, which may cause limitations to its use. Please, contact NFBC project center (NFBCprojectcenter@oulu.fi) and visit the cohort website (www.oulu.fi/nfbc) for more information.

Ethical statement

The study was approved by the ethical committee of the Northern Ostrobothnia Hospital District.

Consent to participate

Written informed consent from both the 15–16-year adolescents and their parents were required.

Consent for publication

The 15–16-year adolescents and their parents gave written consent for publication of study results.

CRediT authorship contribution statement

Study plan: JK, JM, HR, Data-analyses: JK, A-EA, First draft of the manuscript: JK, Critical assessment of the manuscript: JM, HR, EJ, MN, A-EA, NM.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.02.067.

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