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Research paper

Parental age and risk of depression: A nationwide, population-based case-control study

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ABSTRACT

Background: The global prevalence of depression has increased in recent decades and so has the average age of parenthood. Younger and older parental age have been associated with several mental disorders in their offspring, but the associations for depression have been inconsistent.

Methods: This study comprised 37,682 singleton births in Finland from 1987- 2007. The subjects were living in Finland at the end of 2012 and had a depressive disorder recorded in the Care Register for Health Care. We also randomly identified 148,795 controls from the Population Register. When missing obsevations excluded the sample was N_{cases}=18,708 and $N_{controls}$=77,243. The results were adjusted for the parents' psychiatric history, depression history, marital status and place of birth, the mothers' maternal socioeconomic status, smoking during pregnancy and previous births and the children's birth weight.

Results: We found a U-shaped association between offspring depression and the age of both parents. The highest odds of depression occurred when the fathers were aged 50 plus years (adjusted Odds Ratio (ORa) 1.51, 95% CI 1.23-1.86) and the mothers were under 20 (ORa 1.44, 95% CI 1.29-1.60) compared to the reference category of parents aged 25–29 years.

Limitations: The study was limited to depression diagnosed by specialised health care services and had a relatively short follow-up period. Some data were missing and that could lead to risk estimation biases.

Conclusion: Diagnosed depression was higher among the offspring of younger and older parents. The results suggest that the age of the parent is etiologically associated with offspring depression.

1. Introduction

Depression is a serious public health concern and a leading cause of disability worldwide (WHO, 2017). The lifetime prevalence of depression in community-based studies has varied between 4% and 45% (Lim et al., 2018), and the global prevalence has been increasing in recent decades (World Health Organization. Media centre, 2017). Depression has been associated with functional impairment in numerous areas of life, which affects quality of life (Moussavi et al., 2007; Kessler and Bromet 2013; Fried and Nesse 2014). The development of depression involves the interplay of both genetic and environmental risk factors (Saveanu and Nemeroff, 2012).

The average age at which people first become parents has increased significantly, mostly in high-income countries (Svensson et al., 2011). Previous studies have provided good evidence that young, as well as advanced, parental age have been associated with several psychiatric disorders in offspring. Young parental age has been linked with offspring attention deficit hyperactivity disorder (Chudal et al., 2015), psychosis (Miller et al., 2011), bipolar disorder (Chudal et al., 2014) and substance use (McGrath et al., 2014). On the other hand, advanced parental age has been associated with psychosis (Miller et al., 2011; D'Onforio et al., 2014), autism (Hultman et al., 2011; Sandin et al., 2012; D'Onforio et al., 2014), bipolar disorder (Menezes et al., 2010; Chudal et al., 2014, D'Onforio et al., 2014) and suicide attempts (D'Onforio et al., 2014). Several mechanisms have been suggested with regard to both young and advanced parental age and psychiatric illnesses in their offspring Young

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parents themselves often come from economically disadvantaged, less educated families, and are more likely to experience parental absence (Kiernan, 1997; Fergusson and Woodward, 1999; Xu et al., 2018). This can continue to next generation and the shared early life conditions could affect offspring's mental health. Moreover, low family income, parents' unemployment, single parenthood and parental psychopathology have been associated with children's emotional and behavioral problems (Bøe et al., 2012; McLaughlin et al., 2012). Young parental age was also associated with high risk behaviors during pregnancy, including smoking, alcohol use and substance abuse (Merikangas et al., 2017), which could increase the risk of offspring mental disorders later in life (Taylor et al., 2017). Advanced parental age and psychiatric illnesses in their offspring could be related to *de novo* mutations (Malaspina, 2001; Crow, 2003; Flatscher-Bader et al., 2011) and impaired deoxyribonucleic (DNA) repair mechanisms (Bassett et al., 2010). Between 1970 and 2017, delay in childbearing has been observed with the shifts in fertility to later age groups in women in most countries belonging to the Organisation for Economic Co-operation and Development (OECD Social Policy Division 2019). Women aged 30 years or older contributed to 54 percent of total fertility rate in 2015 and 25 percent in the 1970s (Official Statistics of Finland OSF, 2015). In Finland, the mean age of childbirth rose by 4.2 years from 25.4 years in 1982 (Vikat et al., 2002) to 29.6 years in 2019 (Official Statistics of Finland OSF, 2019). It is important to understand the consequences that this sharp rise in parental age at birth may have on their offspring.

Seven studies have examined the association between parental age and offspring depression. Three studies examined the association including both mother and father. Of those, two showed increased odds of offspring depression with only young maternal age and both young and advanced paternal age (McGrath et al., 2014; Fountoulakis et al., 2019). One study demonstrated the association with advanced maternal age (Tearne et al., 2016). One study examined only paternal age and offspring depression and showed increased odds with both young and advanced paternal age (Buizer-Voskamp et al., 2011). One study examined maternal age and depression, and showed that the offspring of the youngest mothers had higher rates of major depression than the offspring of mothers aged over 30 (Fergusson and Woodward, 1999). Two studies did not find any associations (Laursen et al., 2007; Merikangas et al., 2017).

Although there has been evidence of the effect of parental age on offspring depression, the findings have been scarce and inconclusive. These inconsistencies may have been related to methodological differences, such as differences in study populations, sample sizes, covariate selection, the assessment of depression and the age of the offspring at the time of their diagnosis of depression. Apart from the study by McGrath et al. (2014), previous studies did not adjust their results with respect to parental depression and other parental psychiatric illnesses. McGrath et al. (2014) conducted sensitivity analysis controlling for a history of mental illness in a parent or sibling as potential confounders. However, the study included a broad range of mood disorders (F30-F39) together and was sub-analysed only for bipolar disorder. No specific analysis was conducted for major depression in particular.

The aim of the present study was to examine the relationship between paternal and maternal age at childbirth and the risk of depression in their offspring. We did this by using data from Finnish nationwide registers. As the findings related to the effects of parental age have been mixed, we sought to examine any relationships between offspring depression and both young and advanced paternal age and young and advanced maternal age.

2. Methods

This study was based on data from the Finnish Prenatal Study of Depression, which had a nested case-control study design. The study population included all 1,240,062 singleton births in Finland between 1 January 1987 and 31 December 2007 who were still living in Finland at the end of 2012. The study was approved by the Ministry of Social Affairs of Health and the National Institute of Health and Welfare and ethical approval was provided by the Ethics Committee of the Hospital District of Southwest Finland. This study focused on national data on those who had subseqently been diagnosed with depression.

2.1. Cases and controls

Childhood depression was defined using the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) and the later section on adult diagnoses was based on the Eighth Revision (ICD-8). All 37,682 cases of depression were born between 1995 and 2007 and were diagnosed by 31 December 2012. They were identified from the Care Register for Health Care (CRHC) using ICD-9 code 2961 and ICD-10 codes F32.0-F32.9 and F33.0-F33.9. We excluded the cases with severe and profound mental disabilities, using ICD-9 codes 3181 and 3182 and ICD-10 codes F72 and F73. Those diagnosed exclusively with depression before the age of five years and multiple births were also excluded. The 148,795 controls were also singleton children, born alive in Finland during the same study period, without a diagnosis of depression or severe or profound mental disabilities. They were randomly selected from the Finnish Central Population Register (FCPR) and four controls were matched to each case by gender and date of birth (±30 days). The controls had to be alive and living in Finland on the date when the matched cases with depression were diagnosed. Date of birth was used as a matching criterion to control for the prevalence of exposure and depression and to control for confounding by season of birth. We matched by gender to ensure adequate number of males in the study who met the criteria, because of the predominance of depression among females. The controls were excluded from the study if they were from multiple births, they had severe or profound mental retardation or they had a diagnosis of depression or bipolar disorder. Therefore, 1933 controls were excluded from the study and the case to control ratio was not always 1:4.

2.2. Nationwide registers

The CRHC, formerly known as Finnish Hospital Discharge Register, was established in 1969 with a nationwide coverage. Since 1969, it contains complete computerized data of all medical diagnoses in inpatient care, and since 1994 it contains additional information on patient count in inpatient care, policlinics, and specialized outpatient care (Finnish Institute for Health and Welfare., 2020). The data from outpatient visits in hospitals were available from 1998 onwards (Sund et al., 2012). The CRHC was used to identify the cases of offspring depression and parental psychiatric diagnoses. The Finnish Central Population Register (FCPR) contains basic information about Finnish-born citizens and foreign citizens residing permanently in Finland, including their personal identity code. The FCPR was used to identify the matched controls and parental age at the time of delivery. The Finnish Medical Birth Register (FMBR) was established in 1987 and includes comprehensive standardised data on the perinatal and prenatal periods for live or stillborn neonates up to seven days of age (Teperi et al., 1993; (Gissler and Shelley, 2002)). The FMBR was used to identify maternal socio-economic status (SES), marital status, maternal smoking during pregnancy, number of previous births, place of residence at childbirth and the infant's birth weight. Statistics Finland, which was established in 1965 is a public authority that produces official statistics for the country. It was used to obtain information on the source population of the study sample. The personal identity codes of the subjects and their parents were used to link the registers detailed above. The personal identity code is a unique code assigned to all Finnish citizens and foreign residents residing permanently in Finland. Detailed information about the registers and covariates used in Finnish Prenatal Study of Depression have previously been described (Filatova et al., 2019).

2.3. Parental age

The age of the parents was analysed as a categorical variable. Maternal age was classified into the following categories: <20, 20–24, 25–29, 30–34, 35–39, ≥40 years. Paternal age was classified into the following categories: <20, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, ≥50 years. This classification was the same as in previous Finnish prenatal studies on parental age and the risk of mental health disorders (Chudal et al., 2014; Chudal et al., 2015).

To analyse the combined ages of both parents, we created five categories. The reference category was that both parents were 25–34 years and the other categories were: older parents (both parents >34 years), younger parents (both parents <25 years), younger mother but older father (mother <25 and father >34 years) and older mother and younger father (mother >34 and father <25 years). There were 729 and 1484 missing parental age observations in the cases and controls, respectively. Only 13 maternal age observations were missing (12 controls and 1 case). In Finland, paternity is registered automatically if the mother is married. If mothers are unmarried, but cohabiting or in another kind of relationship with the father, paternity can be established by the municipality's child welfare officer. Free DNA testing for paternity is also provided on request.

2.4. Covariates

We selected potential confounders based on previous studies that reported an association between parental age and depression. They included: parental psychiatric history excluding depression (yes/no) (Kessler et al., 2005; Musliner et al., 2015), parental depression history (yes/no) (Kessler et al., 2005; Weissman et al., 2016), maternal SES at childbirth (upper white collar/lower white collar/blue collar worker/other) (Gilman et al., 2002; Vikat et al. 2002), place of residence at childbirth (urban/semi-urban/ rural) (Hoffman et al., 2015), marital status at childbirth (married or in relationship/single) (Bohman et al., 2017), maternal smoking during pregnancy (yes/no) (De Genna et al., 2017; Taylor et al., 2017), number of previous births (0, ≥1) (Riordan et al., 2012; Lahti et al., 2014), birth weight for gestational age (small for gestational age/appropriate for gestational age/large for gestational age) (Kozuki et al., 2013; Goisis et al., 2017; Goisis et al., 2018) and birth year (1987-1993/1994-2000/2001-2007) (McGrath et al., 2014). Parental psychiatric history was defined as a history of any psychiatric disorder, namely ICD-10 codes F0-99, ICD-9 codes 291-316 and ICD-8 codes 291-308 in the CRHC. Parental psychiatric history was classified as yes or no. Parental depression history was derived from the CRHC and based on the following ICD codes: ICD-8 296.00, 298.00, 300.40 and 300.41, ICD-9 2961, ICD-10 F32 and F33. These were then categorised as yes or no. Gestational age was classified in terms of standard deviations from the average reference average weight: small for gestational age was classified as < -2 SD, appropriate for gestational age was -2 SD to +2 SD and large for gestational age was > +2 SD. The covariates were subsequently selected for inclusion in the models if the associations with both parental age and depression were P≤0.1 (Rothman et al., 2008).

There were some missing data for the cases and controls: 0.6% and 0.5% for place of residence, 1.2% and 1% for number of previous births, 1.9% and 1.0% for paternal psychiatric history and paternal depression history, 1.5% and 1.3% for weight for gestational age, 3.2% and 3.0% for maternal smoking, 10.2% and 7.2% for marital status, 44.1% and 43.3% for maternal SES. When we excluded all missing observations the sample reduced to N_{cases}=18,708 and $N_{controls}$=77,243.

2.5. Statistical analyses

The association between covariates and parental age among the controls, and between covariates and depression, were examined by bivariate analysis using Pearson's chi-square test. All variables, except birth year, showed significant associations.

The association between parental age and depression was analysed with conditional logistic regression. In the first unadjusted model, odds ratios (OR) and 95% confidence intervals (CI) were estimated for paternal and maternal age categories.

In the second model, each age category was adjusted for the age of the other parent. Finally, the model was adjusted with all covariates that were significant on bivariate testing (p<0.1). Furthermore, we studied the association between combined ages of both parents and offspring depression in logistic regression and estimated the risk in both unadjusted and adjusted model.

We have also done sensitivity analysis by including and excluding SES from the model adjusted for all other variables in order to compare if missing data bias the results. All statistical analyses were performed with SPSS, version 23 software.

3. Results

The mean age of the onset of depression was 15 years in males and 16 in females. The range of first depression diagnosis was 20 years for both males and females, but standard deviation (SD) was 3.60 for males and 2.47 for females.

The covariates that were associated with both maternal and paternal age and with depression were: maternal depression history, paternal depression history, maternal psychiatric history, paternal psychiatric history, maternal SES, place of residence, marital status, maternal smoking during pregnancy, number of previous births and birth weight for gestational age. All of these covariates were included in the adjusted model. (Supplementary Table 1).

Table 1 shows the parental age distribution in relation to the numbers of controls and individuals with depression. The maternal age of the cases and controls ranged from 14 to 48 years with mean and SD of 28.7 ±5.4 years and 29.1 ±5 years, respectively. The paternal age of the cases ranged from 15 to 66 years (mean 31.2 ±6.23 years) and the controls ranged from 15 to 76 years (mean 31.5 ±5.69 years).

The adjusted analyses showed that the odds of depression were increased among the offspring of both younger and older parents (Table 1). Compared to the reference category of 25–29 years for both sexes, the odds of offspring depression was increased in the maternal age categories of <20, 20–24, ≥ 40 year and in the paternal age categories of <20, 20–24, 35–39, 40–44, 45–49 and ≥ 50 years.

The highest odds of a child developing depression was if their father was aged ≥50 years when they were born (adjusted OR 1.51, 95% CI 1.23-1.86) or if their mother was aged <20 years (adjusted OR 1.44, 95% CI 1.29-1.60).

When the ages of both parents were combined, the findings showed the same risk in most age groups, with a slightly higher odds when both mothers and fathers were less than 25 years old (adjusted OR 1.25, 95% CI 1.20-1.31) (Table 2).

Insert Table 2 here

We also reported the results of sensitivity analysis with inclusion and exclusion of maternal SES in Supplementary Table 2. The association did not differ significantly if SES was included or excluded.

4. Discussion

Both paternal and maternal age were associated with diagnosed depression in their offspring, with the risk increasing at both ends of the parental age spectrum. The offspring of older fathers (≥ 50 years) had a higher risk of depression than fathers aged 25-29 years old, whereas the youngest mothers (<20 years) posed the highest risk in the maternal age categories. However, the effect sizes of the associations that were found in some categories were relatively small.

Table 1
Parental age and risk of diagnosed depression in Finland 1995-2012.

Parental age	Cases (n=18,708) n, %	Controls (n=77,243) n, %	OR (95% CI)	OR (95% CI)[a]	OR (95% CI)[b]
Paternal age groups, (years)					
<20	190 (1)	357 (0.5)	2.27 (1.90-2.71) *	1.97 (1.65-2.36) *	1.45 (1.20-1.76) *
20-24	2215 (11.8)	6664 (8.6)	1.42 (1.34-1.50) *	1.31 (1.24-1.39) *	1.16 (1.10-1.24) *
25-29 (Reference)	5517 (29.5)	23513 (30.4)	1	1	1
30-34	5736 (30.7)	26260 (34)	0.93 (0.89-0.97) *	1.00 (0.95-1.04)	1.00 (0.96-1.05)
35-39	3217 (17.2)	13824 (17.9)	0.99 (0.95-1.04)	1.13 (1.07-1.20) *	1.08 (1.02-1.14) *
40-44	1294 (6.9)	4847 (6.3)	1.14 (1.06-1.22) *	1.36 (1.25-1.47) *	1.22 (1.12-1.32) *
45-49	398 (2.1)	1365 (1.8)	1.24 (1.11-1.40) *	1.51 (1.34-1.71) *	1.31 (1.15-1.49) *
≥50	141 (0.8)	413 (0.5)	1.46 (1.20-1.77) *	1.77 (1.45-2.16) *	1.51 (1.23-1.86) *
Maternal age groups, (years)					
<20	656 (3.5)	1453 (1.9)	2.04 (1.85-2.24) *	2.12 (1.92-2.34) *	1.44 (1.29-1.60) *
20-24	3750 (20)	12330 (16.)	1.37 (1.31-1.44) *	1.40 (1.34-1.47) *	1.21 (1.15-1.27) *
25-29 (Reference)	6397 (34.2)	28885 (37.4)	1	1	1
30-34	5064 (27.1)	23162 (30)	0.99 (0.95-1.03)	0.97 (0.93-1.01)	0.98 (0.94-1.02)
35-39	2267 (12.1)	9389 (12.2)	1.09 (1.03-1.15) *	1.04 (0.98-1.11)	1.02 (0.95-1.08)
≥40	574 (3.1)	2024 (2.6)	1.28 (1.16-1.41) *	1.20 (1.08-1.34) *	1.17 (1.05-1.31) *

* statistically significant (p<0.05);
[a] : adjusted for age of other parent;
[b] : adjusted for age of other parent, maternal depression, parental psychiatric history, maternal SES, place of residence, marital status, maternal smoking during pregnancy, number of previous births and birth weight.

Table 2
Risk of depression associated with age of both parents.

Parental age groups	Cases, (n, %)	Controls, (n, %)	OR (95% CI)[a]	OR (95% CI)[b]
Mother and father <25 years	4777 (25.5)	14983 (19.4)	1.51 (1.46-1.58) *	1.25 (1.20-1.31) *
Mother <25, father >34 years	2774 (14.8)	11198 (14.5)	1.18 (1.12-1.23) *	1.11 (1.06-1.17) *
Mother >34, father <25 years	607 (3.2)	2293 (3)	1.26 (1.15-1.38) *	1.11 (1.01-1.23) *
Mother and father 25–34 years	8398 (44.9)	39891 (51.6)	1	1
Mother and father >34 years	2152 (11.5)	8878 (11.5)	1.15 (1.09-1.21) *	1.12 (1.06-1.18) *

[a] : unadjusted model;
[b] : adjusted for parental depression, parental psychiatric history, maternal socioeconomic status, place of residence, marital status, maternal smoking during pregnancy, number of previous births and birth weight
* statistically significant (p<0.05); OR: odds ratio; CI: confidence interval

4.1. Paternal age

There was a U-shaped association for paternal age and depression (Table 1). Our results were in line with two register-based studies (Buizer-Voskamp et al., 2011; McGrath et al., 2014) and another case-control study (Fountoulaksis et al., 2019) that found that the offspring of the youngest and oldest fathers had the highest risk of depression. However, another Danish study found no association between offspring depression and paternal age (Laursen et al., 2007). It should be noted that Laursen et al. (2007) studied a younger age group and used 20–25 years as the reference category compared to 25–29 years in the present study. Studies based on populations in the United States (Merikangas et al., 2017) and Australia (Tearne et al., 2016) did not find any significant associations with paternal age. The former used the Kiddie-Schedule for Affective Disorders and the latter used the Depression Anxiety Stress Scales, but only included female offspring. The differences in the target populations in terms of clinical diagnoses, population size and measurement scales may explain the differences in the results between these two studies and the present study.

4.2. Maternal age

We found that both lower (<20 and 20–24 years) and higher (≥40 years) maternal age were linked with offspring depression. Previous studies have reported similar findings. For example, McGrath et al. (2014) showed that younger maternal age (12–19 and 20–24 years) were associated with mood disorders in offspring. Similar findings were also reported from New Zealand (Fergusson and Woodward, 1999) and the United States (Merikangas et al., 2017). A Western Australia study reported an association with higher maternal age of ≥ 35 years (Tearne et al., 2016). Only McGrath et al. (2014) was a register-based study, while the others used symptom scales for to diagnose depression. However, McGrath et al. (2014) included a broad range of depression diagnoses (ICD-10 F30-F39, excluding bipolar) compared to the present study, where only diagnoses of depressive episodes or recurrent depression were studied (ICD-10 F32 and F33 and ICD-9 2961).

We also found that offspring of mothers aged 30-34 and 35-39 years old did not have increased risk of depression, while maternal age over 40 years was a significant predictor. Increased maternal age has been shown to be associated with such protective factors as increased SES (Myrskylä and Fenelon, 2012), better maternal education(Mofitt, 2002) and more supportive home environment (Fergusson and Woodward et al., 1999). On the other hand, advanced maternal age is associated with increased risk of obstetric and perinatal complication (Tarín et al., 1998; Batstra et al., 2006). Therefore, probably, while negative effects of middle age motherhood can be toned down by these sociodemographic factors, it cannot absolutely overweight the biological consequences related to older motherhood.

4.3. Possible mechanisms

4.3.1. Older parenthood

The number of women who have their first baby at 35–40 years of age has increased in Western countries and advanced maternal age has often been associated with advanced paternal age (Heffner, 2004). Previous studies have suggested several mechanisms to explain the link between advanced paternal age and mental health problems in their offspring (Buizer-Voskamp et al., 2011; McGrath et al., 2014; Chudal et al., 2014; Chudal et al., 2015; Tearne et al., 2016; Merikangas et al., 2017). First, the association may be related to an increased number of *de novo* mutations (Malaspina, 2001; Crow, 2003; Flatscher-Bader et al., 2011), to impaired DNA repair mechanisms (Bassett et al., 2010), to altered brain structure (Foldi et al., 2010) and to altered behaviour in

the offspring, which has been observed in mice (Smith et al., 2009; Foldi et al., 2010). It has also been shown that the *de novo* mutations explain the association between parental age and advanced maternal age (Goldmann et al., 2016). Indeed, genetic vulnerability might play a role in the development of mental health problems. For example, older fathers may have personality traits that make it difficult to build relationships and this would increase the risk of psychiatric disorders in their offspring (Zammit et al., 2003). We can speculate that such personality traits could also have the same effect on older mothers.

In general, the reasons behind the association between advanced maternal age and offspring depression are not as well established as for paternal age. On the one hand, advanced maternal age has been associated with an increased risk of obstetric and perinatal complications that are linked with depression (Tarín et al., 1998; Batstra et al., 2006). Increasing maternal age also affects endocrine and hormonal factors, which may lead to offspring depression due to maternal stress (Weinstock, 2010). These factors may result in the need for infertility treatment which has been associated with obstetric complications (Sazonova et al., 2011). On the other hand, older mothers can have a better SES and access to greater resources and these may protect their offspring against depression (Myrskylä and Fenelon, 2012). However, when we look at the overall picture, it is still unclear what ultimately gives rise to the association between advanced maternal age and depression in their offspring.

Accumulated exposure to various environmental toxins over time can influence genomic and epigenetic alterations in the germ cells of older parents. These toxins can result in DNA damage, germline mutations and global hypermethylation in germ cells and this may have long-term negative effects on the offspring (Williams and Ross, 2007; Yauk et al., 2008). Multiple episodes of exposure to toxins may raise the risk of depression, as the additive effect of shared pathways involving genetic, epigenetic, hormonal and environmental factors, may be transferred by older parents (Shelton et al., 2010; Buizer-Voskamp et al., 2011).

Some researchers have proposed that generational differences between mothers and their children may results in tension in the parent-child relationship during adolescence. This can have a negative impact on the transition from adolescence to adulthood, which in itself is often associated with stress, anxiety and low moods. This has been shown to particularly apply to mother-daughter relationships (Tearne et al., 2016), but may also apply to mother-son and father-child relationships. Higher parental age has also been associated with the increased prevalence of parental illnesses, including cancer, heart disease and chronic respiratory diseases, which could be very stressful for their children (Osborn, 2007; Merikukka et al., 2018). This may obviously increase the risk of mental health problems in their offspring.

4.3.2. *Young parenthood*

Young parenthood may be the result of unplanned pregnancy. This can have an impact on education and employment and increases the risk of socioeconomic exclusion and of a broad range of adverse outcomes in the offspring, such as health, education and criminal behaviour (Mills et al., 2011). This can continue to the next generation, as young parents often come from economically disadvantaged and less educated families (Kiernan, 1997; Fergusson and Woodward, 1999). Young parents may also have traits like low impulse control and high risk-taking behaviour, involving alcohol and illicit drug abuse and smoking, which the offspring is exposed to (Merikangas et al., 2017). Risky health-related behaviours (Little and Sing, 1986; Spingarn and DuRant, 1996; Vine, 1996) and low use of prenatal care services (Kiernan, 1997; D'Askoli et al., 1997) can lead to adverse reproductive outcomes that have been associated with the etiology of depression, like low birth weight (Loret de Mola et al., 2014). These early life stresses are likely to cause functional and structural impairment in brain development. Children exposed to severe early life stress have been shown to experience deficits in affective and cognitive functioning, which may contribute to the progression of mental illness such as mood disorders (Gunnar and Quevedo, 2007; Pechtel and Pizzagalli, 2011).

4.3.3. *Strengths and limitations of the study*

The strengths of this study were the large population sample, the extensive linked data on outcomes and the fact that exposure and covariates were collected from several high-quality registers. In comparison to previous register-based studies based on diagnoses from psychiatric registers (Laursen et al., 2007; Buzer-Voskamp et al., 2011; McGrath et al., 2014), the Finnish CRHC records depression diagnoses from a broad range of specialised services. In addition, this study included a substantial number of covariates that were lacking in previous studies.

There were some limitation to the study that need to be taken into consideration. Firstly, the study sample only included depression diagnosed by specialised health care services, but it did not included primary health care diagnoses. This means that we identified the most severe cases of depression in the population, but probably missed less severe cases. Secondly, hospital-based clinical diagnoses for depression were recorded in the CRHC and these may have had lower diagnostic validity than standardised interviews. However, studies have reported that the validity of the CRHC for psychiatric diagnoses was good (Keskimäki and Aro, 1991; Sund, 2012). Thirdly, there were also some missing data on covariates and exposures, which may have led to risk estimation biases. Fourthly, the outpatient data were not available until 1998, which may have resulted in some missing cases of parental and children's depression diagnosis. Lastly, the study design only included children and young adults aged 5-25 with a diagnosis of depression and some cases may have been missed due to the relatively short follow-up time.

5. Conclusions

This study found an increased risk of diagnosed depression in the offspring of both younger and older parents. The findings suggest that the age of a parent plays a role in the etiology of depression in their offspring, but further studies are required before we can understand the biological and social mechanisms underlying those effects. These findings are relevant to the global changes in the ages at which men and women become parents. This can contribute to increased awareness about the effect of parental age on offspring depression and identification of individual at risk of depression at an earlier age.

Author disclosure

Contributors

Dr Svetlana Filatova and MPh Subina Upadhyaya conducted the investigation, writing original draft, reviewing and editing. Dr Filatova also conducted formal analysis. Dr Roshan Chudal advised on methodology and supervised the project. Dr Terhi Luntamo contributed with reviewing the draft. Professor Andre Sourander contibuted with the data curation, conceptualization, project administration and funding acquisition.

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Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.12.197.

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