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Association of adolescent depression with subsequent prescriptions of anti-infectives and anti-inflammatories in adulthood: A longitudinal cohort study

Richard Ssegonja [a,b,*], Iman Alaie [c,d], Amanda Holmgren [d], Hannes Bohman [d], Aivar Päären [d], Lars von Knorring [e], Anne-Liis von Knorring [d], Ulf Jonsson [d,f,g]

[a] Department of Public Health and Caring Science, Uppsala University, Uppsala, Sweden
[b] Department of Medical Sciences, Respiratory, Allergy- and Sleep Medicine Research Unit, Uppsala University, Uppsala, Sweden
[c] Division of Insurance Medicine, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[d] Department of Medical Sciences, Child and Adolescent Psychiatry, Uppsala University, Uppsala, Sweden
[e] Department of Medical Sciences, Psychiatry, Uppsala University, Uppsala, Sweden
[f] Centre of Neurodevelopmental Disorders (KIND), Centre for Psychiatry Research, Department of Women's and Children's Health, Karolinska Institutet & Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden
[g] Child and Adolescent Psychiatry, Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden

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ABSTRACT

New insights into how depression is linked to physical health throughout the lifespan could potentially inform clinical decision making. The aim of this study was to explore the association of adolescent depression with subsequent prescriptions of anti-infectives and anti-inflammatories in adulthood. The study was based on the Uppsala Longitudinal Adolescent Depression Study (ULADS), a Swedish prospective cohort study initiated in 1991. Depressed ($n = 321$) and non-depressed ($n = 218$) adolescents were followed prospectively using patient registries. The associations of adolescent depression (age 16–17 years) with subsequent prescription of anti-infectives and anti-inflammatories (age 30–40 years), were analysed using generalized linear models. Sub-analyses explored the impact of diagnostic characteristics in adolescence and reception of anti-depressants prescriptions in adulthood. The results suggest that females with persistent depressive disorder in adolescence have a higher rate of future prescriptions than non-depressed peers, with adjusted incidence rate ratio of 1.42 (1.06 to 1.92) for anti-infectives and 1.72 (1.10 to 2.70) for anti-inflammatories. These associations were mainly driven by those who were also prescribed antidepressants during the same period. Associations were less robust for females with episodic or subsyndromal depression in adolescence and for males. These findings emphasize the importance of integrated mental health services at the primary healthcare level.

1. Introduction

Depressive disorders constitute a major public health concern, contributing considerably to the global burden of disease (Institute for Health Metrics and Evaluation (IHME), 2016). Estimates of the lifetime prevalence of depression across cultures suggest that at least one in every ten individuals are expected to experience a depressive episode in the course of their life (Kessler and Bromet, 2013). A noticeable proportion of individuals report commencement of the disorder in adolescence (Kessler et al., 2005), raising important questions about health-related outcomes later in life.

While it is well established that adolescent depression is linked to continued mental health problems in adulthood (Johnson et al., 2018), the association with subsequent physical health has been studied to a lesser extent. However, a recent Swedish registry study clearly suggests an association of severe early-onset depression with subsequent somatic disease (Leone et al., 2021). Furthermore, adult depression frequently co-occurs with a range of general medical conditions (Dhar and Barton, 2016; Gaspersz et al., 2018; Goodwin G M, 2006; Hare et al., 2014; Osborn, 2001; Voinov et al., 2013). Meta-analytic studies have, for instance, shown an association with heart disease (Nicholson et al., 2006), diabetes (Mezuk et al., 2008), hypertension (Meng et al., 2012),

* Corresponding author at: Department of Public Health and Caring Sciences, Uppsala University, Husargatan 3, 75122 Uppsala, Sweden.
E-mail address: richard.ssegonja@pubcare.uu.se (R. Ssegonja).

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stroke (Dong et al., 2012) and obesity (Luppino et al., 2011). This comorbidity pattern imposes a burden on primary care facilities in particular, where a large proportion of patients with mental health conditions and acute or chronic but stable somatic ailments are managed (Lejtzen et al., 2014; Olfson, 2016; Sundquist et al., 2017).

The pathophysiology and mechanisms behind the susceptibility of depressed individuals, or those with a history of depression at some point in life, to develop poor mental and physical health later in life are still poorly understood. However, research suggests a link between depression and immunoinflammatory dysregulation (Brod et al., 2014; Penninx et al., 2013), partly through the increased release of stress hormones and dysregulation of the hypothalamic-pituitary-adrenal axis (Bauer, 2005; Penninx et al., 2013; Zunszain et al., 2011). This could render depressed individuals vulnerable to physical ill health such as infectious diseases (Andersson et al., 2015, 2016). Other literature brings forth a link between depression and chronic inflammation, as evidenced by research on pro-inflammatory cytokines (Brod et al., 2014; Felger and Lotrich, 2013; Myint and Kim, 2003; Penninx et al., 2013), as an alternative explanation, especially for inflammatory and auto-immune disorders (Euesden et al., 2017). Conversely, somatic medical illnesses including infectious diseases as well as auto-immune/inflammatory disorders are also a documented risk factor for depression (Euesden et al., 2017; Kostev et al., 2019; Köhler-Forsberg et al., 2019). Hence there is a two-way directional relationship in the occurrence of events.

Against this background, it is important to better understand the possible pathways connecting early onset mental health problems and physical ill-health from a life course perspective. It is possible that early onset depression might affect an individual immunologically far beyond the duration of the depressive symptoms, as demonstrated in the vulnerability to infections in previous research (Andersson et al., 2015). Such a sustained effect might be further augmented by the stress and strain of socioeconomic circumstances in the wake of early onset depression (Alaie et al., 2021; Clayborne et al., 2019; Philipson et al., 2020). It is equally plausible, however, that residual symptoms and recurrent depressive episodes in adulthood (Jonsson et al., 2011b) lead to an increased susceptibility to infections throughout the lifespan.

Our research group has in earlier work used the Uppsala Longitudinal Adolescent Depression Study (ULADS) (Alaie et al., 2019), a community cohort of depressed adolescents and non-depressed peers followed into adulthood, to explore the relationship between adolescent depression and healthcare consumption, including prescribed medication in adulthood (Päären et al., 2012; Ssegonja et al., 2019). Higher numbers of prescriptions were observed in depressed females compared to the non-depressed individuals at age 29–31, especially for anti-infectives, anti-mycotics and anti-inflammatories (Päären et al., 2012). However, several clinically relevant questions still remain, including whether these associations persist over time and to what extent these associations are driven by subgroups of females with more severe forms of depression and continued mental health problems in adulthood. Recent costing analyses based on the same cohort suggest that healthcare consumption in adulthood and associated costs might be particularly high for individuals with a history of persistent depressive disorders in adolescence. While the added costs for psychiatric care were partially mediated by recurrence of depression in early adulthood, somatic care was not (Ssegonja et al., 2019). Thus, the heterogeneity of adolescent depression in terms of duration and recurrence throughout the lifespan seems to be a key to better understand associations with subsequent health.

To facilitate more personalized treatment for young people with depression, it is important to obtain more detailed information about the association of early onset depression and physical health. In the present study, we therefore set out to further explore these associations. To mirror the vulnerability to infections and inflammatory/autoimmune disorders, we chose to focus on prescriptions for anti-infectives and anti-inflammatories (bearing in mind that some of these medications can still be obtained over the counter without prescriptions). This work examined the relationship between adolescent depression, receipt of prescriptions of anti-depressants in adulthood (a possible proxy for mental health problems) and the frequencies of anti-infectives and anti-inflammatories prescriptions in adulthood. In order to add to the sparse literature on longer-term outcomes of adolescent depression, we explicitly focused on outcomes beyond the transitional phase of young adulthood. We hypothesized that individuals with a more persistent course of depression would also have higher rates of prescriptions of anti-infectives and anti-inflammatories. Three specific research questions were addressed:

1 To what extent is adolescent depression associated with prescription of anti-infectives and anti-inflammatories in adulthood (age 30 to 40 years)?
2 Does the strength of these associations vary depending on the characteristics/clinical subtype of the depressive disorder experienced in adolescence?
3 To what extent are these associations related to reception of anti-depressants prescriptions during the same phase of adulthood (age 30 to 40 years)?

2. Methods

2.1. Study design

This work stems from a prospective epidemiological cohort study initiated in 1991, the Uppsala Longitudinal Adolescent Depression Study (ULADS) and our earlier work on the subject (Alaie et al., 2019; Päären et al., 2012; Ssegonja et al., 2019). First-year students starting upper-secondary school in Uppsala, Sweden, were screened for depression using self-rated questionnaires in 1991–1993. Adolescents with a positive screen profile, and peers matched for sex, age and school year/class, were invited for a diagnostic interview. Participants have thereafter been followed up through interviews and national registries. The cohort has been profiled in detail elsewhere (Alaie et al., 2019). The research reported here was granted ethical approval by the Regional Ethical Review Board in Uppsala (2015/449/1–2).

2.2. Participants and procedure

All adolescents aged 16–17 years starting upper secondary school in Uppsala during one school year were invited. Of the invited individuals, 93% (n = 2300) agreed to participate in the screening. Depression screening was conducted using two self-rated tools, Beck depression inventory – Child (BDI-C) (Beck et al., 1961) and the center for Epidemiological Studies Depression Scale (CES-DC) (Schoenbach et al., 1982). All positive screen individuals, defined as BDI-C $\geq$ 16 or CES-DC $\geq$ 30 + BDI-C $\geq$ 11 or a self-reported suicide attempt, were invited for a structured diagnostic interview. A total of 355 (77% females) adolescents screened positive. For every positive screen, a negative screen peer, matched for age, sex and school year from the same school and class was also invited for the diagnostic interview, creating a total of 710 (77% females) altogether. Of the 710 participants, 631 (78% females) participated in the diagnostic interviews.

Data on healthcare consumption up to year 2016 was retrieved from national registers (n = 576; 79% females), excluding individuals who at baseline did not give consent to further participation subsequently had refused extraction of individualized registry data. Individuals that met the criteria for a hypomanic or manic episode at baseline (n = 37) were excluded, due to the difference in symptom profiles and prognosis between bipolar and depressive disorders. This left an analytic sample of 539 (79% females) for this work (see Fig. S1 in the supplementary appendix).

2.3. Study variables

2.3.1. Adolescent depression

This was the exposure variable of interest. The depressed adolescents at baseline were categorized into clinical subtypes of depressive disorders by applying the current Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria (American Psychiatric Association, 2013) to the original Diagnostic Interview for Children and Adolescents in the revised form (DICA-R-A) (Reich et al., 1982) diagnoses. This was done in order to conform to the current diagnostic terminology. The following diagnostic subgroups were defined:

Persistent depressive disorder (PDD): depressed mood occurring for most of the day, for more days than not, for at least one year. The disorder subsumes previous DSM-III- R and DSM-IV definitions of chronic major depressive disorder and dysthymic disorder ($n = 175$);

Episodic major depressive disorder (MDD): a current or life-time major depressive episode lasting shorter than one year ($n = 82$);

Subthreshold depression: a positive screening but no past or current depressive episode ($n = 64$);

No depression: negative screening, no past or current depressive disorder ($n = 218$).

2.3.2. Adolescent comorbidities

Disruptive behaviour disorder (dichotomized) was defined as a childhood or adolescent DSM-III-R diagnosis of conduct disorder, oppositional-defiant disorder, and/or attention deficit/hyperactivity disorder according to DICA-R-A. Childhood or adolescent anxiety disorder (dichotomized) was defined as a childhood or adolescent DSM-III-R diagnosis of separation anxiety disorder, overanxious disorder, and/or avoidant disorder according to DICA-R-A.

Chronic somatic disorders in childhood and adolescence were defined as a chronic somatic illness that was captured in the national patient registry during the period around the baseline assessment (1992 to 1996). These included diagnoses such as diabetes mellitus, epilepsy, and cardiac septal defects. The variable was dichotomized as a "yes" (1) to imply presence of at least one chronic somatic disorder and "no" (0) for its absence.

2.3.3. Socioeconomic status

To reflect the socioeconomic status at baseline, the highest level of education of either parent based on information from statistics Sweden was used. The variable was dichotomized as high, for those that attained tertiary education and low for those that did not.

2.3.4. Prescriptions of anti-infectives and anti-inflammatories

Data on consumption of prescribed medication was retrieved from the Swedish Prescribed Drug Register, hosted by The National Board of Health and Welfare. The register provides information about prescription date, medicine anatomical therapeutic classification (ATC) codes (WHO Collaborating Centre for Drug Statistics Methodology, 2022), amount, and cost with coverage from 2005. Data on prescriptions for anti-infectives (ATC codes: J01 – antibacterial, J02 – antimycotics, J04 – antimycobacterial, J05 – antivirals, and J06B – immunoglobulins) and anti-inflammatories (M01A – non-steroidal anti-inflammatory and antirheumatic agents, M01B – combined anti-inflammatory and antirheumatic agents, and M01C – specific anti-rheumatic agents), and was available for the period mid-2005 to 2016 (approximately age 30 to 40 years). The retrieved data was used to estimate prescription frequencies across the follow-up period.

2.3.5. Treatment for common mental disorder in adulthood

Prescriptions for antidepressants (ATC code: N06A) drug in the years 2005 to 2016 was retrieved from the same registry and were viewed as a proxy indicator of ongoing treatment for a common mental disorder (e.g., depressive disorders and anxiety disorders) during the same phase of adulthood (age 30 to 40).

2.4. Statistical analysis

2.4.1. Descriptives

Baseline characteristics and observed outcomes for the defined groups were summarized as counts and percentages for categorical variables, mean counts, and standard deviations for the numerical variables across the follow-up period.

2.4.2. Exposure effect analysis

The relationship between adolescent depression and differences in mean frequency/count of anti-infectives and anti-inflammatories prescriptions was examined using regression analysis, generalized linear models. To accommodate the distributional properties of count data, a quasi-poisson distribution and a log link function were used. All analyses were conducted comparing the depressed to their non-depressed counterparts as at baseline while adjusting for age, adolescent chronic somatic disorder, socioeconomic status, comorbid anxiety disorders and disruptive behaviour disorder. These covariates were selected based on their potential relevance for the investigated association. Immune status and risk of depression varies with age, while all the remaining covariates were deemed to be potential risk factors of adolescent depression, continued mental health problems, and susceptibility to inflammatory/autoimmune and/or infectious diseases. The effect measure of the relationship was expressed as an incidence rate ratio (IRR).

2.4.3. Sensitivity analysis

In case a significant association was observed between any of the sub-categories of adolescent depression and subsequent overall prescription of either anti-infectives or anti-inflammatories, sensitivity analyses were conducted to explore whether this association depended on continued mental health problems in adulthood. Using presence of a prescription for antidepressants in adulthood (age 30 – 40 years) as a proxy for presence of a common mental disorder, the following subgroups were formed:

- No adolescent depression and no common mental disorder between ages 30 – 40 years
- No adolescent depression, but a common mental disorder between ages 30 – 40 years
- Adolescent depression, but no common mental disorder between ages 30 – 40 years
- Adolescent depression and a common mental disorder between ages 30 – 40 years

Using these sub-groups, the exposure effect analyses to examine differences in the mean number of anti-infectives and anti-inflammatories prescriptions were conducted with *no adolescent depression and no common mental disorder* (no receipt of antidepressants prescriptions) *between ages 30 – 40 years* as the reference group.

The specific anti-infectives usually prescribed for the common sexually transmitted diseases (Doxycycline, ATC number J01AA02, for Chlamydial infections and Fluconazole for vaginal candidiasis, ATC number J02AC01) were explored in sub-analyses, since young people with depression might be at increased risk of sexually transmitted infections (Jonsson et al., 2011a). Note that these medications are also prescribed for other conditions and thus, sexually transmitted infections are simply used as examples in this case as it was not possible to identify the indication for the prescriptions in the dataset.

All results are presented separately for females and males given the different help seeking behaviours (Thompson et al., 2016), and for the three subgroups of adolescent depression as earlier literature documents different prognoses (Jonsson et al., 2011b). All analyses were conducted in R version 4.0.0 with statistical significance set at $p < 0.05$.

3. Results

3.1. Descriptives

Adolescent psychiatric conditions and adult prescriptions of anti-infectives and anti-inflammatories are summarized descriptively in Table 1. Disruptive disorders and anxiety disorders in childhood or adolescence were highly prevalent amongst both male and female populations with adolescent depression, as compared to the non-depressed peers. There was no consumption of antimycobacterial, immunoglobulins and specific anti-rheumatic agents.

3.2. Exposure effect analysis

3.2.1. Anti-infectives (anti-bacterials, anti-mycotics and anti-virals)

amongst females, adolescent depression was associated with a higher rate of anti-infectives prescriptions in adulthood (age 30–40 years), aIRR 1.24 (0.95 – 1.61) $p = 0.114$, though not statistically significant. However, significant findings were noted with the breakdown to the individual anti-infectives categories: anti-bacterials, aIRR 1.28 (1.01 – 1.63) $p = 0.0442$, and anti-mycotics, 2.11 (1.15 – 4.10) $p = 0.0209$. The noted difference was more pronounced in the PDD group. The results in the male population were rather unclear, possibly owing to the relatively small numbers of participants. However, adolescent PDD was associated with a significantly lower rate of prescriptions of anti-infectives, aIRR 0.43 (0.20 - 0.86) $p = 0.0237$, in adulthood amongst males (see Table 2). The results also demonstrate an increased rate of prescriptions for fluconazole in the females with adolescent depression compared to the no depression group. This was true for PPD and Episodic MDD but not subsyndromal depression. However, the results for prescriptions of Doxycycline were non-significant. See supplementary tables S1-S4 in the appendix for details on all anti-infectives.

3.2.2. Anti-inflammatories

Females with adolescent depression at baseline received more anti-inflammatories prescriptions in adulthood (age 30–40 years) compared to the non-depressed, aIRR 1.49 (1.02 – 2.21), $p = 0.045$. This relationship was sound for the PDD group, aIRR 1.72 (1.10 – 2.70), $p = 0.0172$. Same direction of findings was noted in the male population though non-significant as in most of the anti-infectives (Table 2 and supplementary tables S5-S11).

3.3. Sensitivity analyses

PDD was the only subtype of adolescent depression which was significantly associated with the overall adult prescription of either anti-infectives or anti-inflammatories. This was true for both females and males, albeit with a reversed association in males. Further exploration of this subgroup showed that female participants with PDD and a prescription of antidepressants between ages 30 – 40 years group, were prescribed more anti-infectives and anti-inflammatories in adulthood compared to the group with no depression at either time points. The noted relationship remained after adjustment for observed confounders. For the group with no depression in adolescence, but prescriptions of antidepressants in adulthood, a similar pattern to that in the group with PDD and adulthood reception of antidepressants prescriptions was seen only for anti-inflammatories. The findings in the male population were largely non-significant. See Tables 3, 4 and supplementary tables S12-S18 for details.

4. Discussion

4.1. Summary of results

This study investigated the relationship between adolescent

Table 1
Descriptive statistics of the sample.

Variable			Subtypes of adolescent depression		
Females	No depression in adolescence ($n = 171$) Counts (%) & mean (SD)	Depressed in adolescence ($n = 254$) Counts (%) & mean (SD)	PDD($n = 140$) Counts (%) & mean (SD)	Episodic MDD ($n = 68$) Counts (%) & mean (SD)	Subsyndromal ($n = 46$) Counts (%) & mean (SD)
Disruptive behaviour disorders	12 (7%)	66 (26%)	43 (31%)	13 (19%)	10 (22%)
Anxiety disorders	27 (16%)	116 (46%)	87 (62%)	25 (37%)	4 (9%)
Chronic somatic disorder	12 (7%)	29 (11%)	15 (11%)	9 (13%)	5 (11%)
High parental education	82 (48%)	114 (45%)	69 (49%)	25 (36%)	20 (43%)
Medication type (prescriptions)					
Anti-Infectives	4.94 (5.95)	6.41 (7.80)	7.18 (9.50)	5.87 (5.03)	4.87 (4.60)
Antibacterials	3.58 (3.74)	4.84 (5.57)	5.01 (6.42)	4.91 (4.44)	4.22 (4.14)
Antimycotics	0.44 (1.37)	0.94 (2.46)	1.13 (2.90)	0.91 (2.12)	0.41 (1.07)
Antivirals	0.92 (4.06)	0.63 (3.49)	1.04 (4.64)	0.04 (0.21)	0.24 (0.95)
Anti-inflammatories	1.63 (3.79)	2.24 (3.55)	2.37 (3.73)	1.96 (2.90)	2.26 (3.90)
Males	**No depression in adolescence ($n = 47$)** Counts (%) & mean (SD)	**Depressed in adolescence ($n = 67$)** Counts (%) & mean (SD)	**PDD ($n = 35$)** Counts (%) & mean (SD)	**Episodic MDD ($n = 14$)** Counts (%) & mean (SD)	**Subsyndromal ($n = 18$)** Counts (%) & mean (SD)
Disruptive behaviour disorders	4 (9%)	30 (45%)	17 (49%)	7 (50%)	6 (33%)
Anxiety disorders	5 (11%)	29 (43%)	18 (51%)	9 (64%)	2 (11%)
Chronic somatic disease	3 (6%)	3 (4%)	2 (6%)	0	1 (6%)
High parental education	26 (55%)	32 (48%)	20 (57%)	6 (43%)	6 (33%)
Medication type (prescriptions)					
Anti-Infectives	3.55 (6.40)	2.46 (2.79)	1.94 (2.09)	2.93 (2.84)	3.11 (3.77)
Antibacterials	2.94 (4.53)	2.40 (2.73)	1.86 (2.09)	2.93 (2.84)	3.06 (3.57)
Antimycotics	0.02 (0.15)	0	0	0	0
Antivirals	0.60 (2.65)	0.06 (0.24)	0.09 (0.28)	0	0.06 (0.24)
Anti-inflammatories	1.00 (1.74)	1.67 (2.90)	2.03 (3.72)	1.93 (1.59)	0.78 (1.35)

Abbreviations: PDD, Persistent Depressive Disorder; MDD, Major Depressive Disorder.

Table 2
Relationship between adolescent depression and prescription of anti-infectives and anti-inflammatories in adulthood (age 30–40 years).

Medication type	Any depression aIRR (95% CI)	PDD aIRR (95% CI)	Episodic MDD aIRR (95% CI)	Subsyndromal aIRR (95% CI)	No depression aIRR (95% CI)
Females					
Anti-Infectives	1.24 (0.95 – 1.61)	**1.42* (1.06 – 1.92)**	1.17 (0.82 – 1.66)	0.97 (0.62 – 1.46)	Reference
Antibacterials	**1.28* (1.01 – 1.63)**	1.32 (1.00 – 1.76)	1.33 (0.96 – 1.81)	1.14 (0.78 – 1.65)	Reference
Antimycotics	**2.11* (1.15 – 4.10)**	**2.72** (1.38 – 5.51)**	**2.29* (1.05 – 4.90)**	0.96 (0.27 – 2.68)	Reference
Antivirals	0.68 (0.24 – 1.89)	1.27 (0.50 – 3.17)	0.05 (0.00 – 0.66)	0.27 (0.01 – 1.51)	Reference
Anti-inflammatories	**1.49* (1.02 – 2.21)**	**1.72* (1.10 – 2.70)**	1.25 (0.72 – 2.10)	1.37 (0.75 –2.40)	Reference
Males					
Anti-Infectives	0.63 (0.35 – 1.11)	**0.43* (0.20 – 0.86)**	0.57 (0.23 – 1.32)	0.97 (0.46 –1.91)	Reference
Antibacterials	0.78 (0.45 – 1.35)	0.55 (0.27 – 1.08)	0.82 (0.35 – 1.81)	1.10 (0.55 – 2.08)	Reference
Antimycotics	_	_	_	_	Reference
Antivirals	_	_	_	_	Reference
Anti-inflammatories	1.29 (0.62 – 2.83)	1.63 (0.72 – 3.75)	1.44 (0.49 – 4.00)	0.72 (0.19 – 2.19)	Reference

Note: All analyses were adjusted for age, adolescent chronic somatic disorder, socioeconomic status, and childhood or adolescent anxiety disorders and disruptive behaviour disorder.
Abbreviations: PDD, Persistent Depressive Disorder, MDD, Major Depressive Disorder; aIRR: adjusted Incidence Rate Ratio; CI, Confidence Interval.
* $p<0.05$,.
** $p<0.01$ and
*** $p<0.001$.

Table 3
Descriptive statistics in subgroups based on the presence or absence of persistent depressive disorder (PDD) in adolescence and receipt of anti-depressants prescriptions (RAP) in adulthood (age 30–40 years).

Variable	Group categories			
Females	No adolescent depression & no RAP between ages 30 - 40 ($n = 129$) Counts (%) and mean (SD)	No adolescent depression, but RAP between ages 30 - 40 ($n = 42$) Counts (%) and mean (SD)	Adolescent depression (PDD), but no RAP between ages 30 - 40 ($n = 78$) Counts (%) and mean (SD)	Adolescent depression (PDD) & RAP between ages 30 - 40 ($n = 62$) Counts (%) and mean (SD)
Disruptive behaviour disorders	7 (5%)	5 (12%)	25 (32%)	18 (29%)
Anxiety disorders	15 (12%)	12 (29%)	43 (55%)	44 (71%)
Chronic somatic disease	8 (6%)	4 (10%)	8 (10%)	7 (11%)
Parental education	62 (48%)	20 (48%)	39 (50%)	30 (48%)
Disposable income (parents)	87 (67%)	22 (52%)	44 (56%)	41 (66%)
Medication type (prescriptions)				
Anti-Infectives	4.69 (6.04)	5.71 (5.65)	4.29 (3.97)	10.81 (12.72)
Antibacterials	3.36 (3.59)	4.29 (4.15)	3.45 (3.23)	6.98 (8.59)
Antimycotics	0.36 (1.20)	0.69 (1.80)	0.62 (1.39)	1.77 (3.99)
Antivirals	0.98 (4.39)	0.74 (2.84)	0.23 (0.79)	2.05 (6.81)
Anti-inflammatories	1.13 (2.06)	3.14 (6.57)	1.58 (2.65)	3.37 (4.58)
Males	**No adolescent depression & no RAP between ages 30 - 40 ($n = 36$)**	**No adolescent depression, but RAP between ages 30 - 40 ($n = 11$)**	**Adolescent depression (PDD), but no RAP between ages 30 - 40 ($n = 22$)**	**Adolescent depression (PDD) & RAP between ages 30 - 40 ($n = 13$)**
	Counts (%) and mean (SD)	Counts (%) and mean (SD)	Counts (%) and mean (SD)	Counts (%) and mean (SD)
Disruptive behaviour disorders	3 (8%)	1 (9%)	11 (50%)	6 (46%)
Anxiety disorders	3 (8%)	2 (18%)	11 (50%)	7 (54%)
Chronic somatic disease	3 (8%)	0	2 (9%)	0
Parental education	20 (56%)	6 (55%)	12 (55%)	8 (62%)
Disposable income (parents)	25 (69%)	8 (73%)	10 (45%)	9 (69%)
Medication type (prescriptions)				
Anti-Infectives	2.94 (4.27)	5.55 (10.91)	1.82 (2.26)	2.15 (1.82)
Antibacterials	2.44 (2.76)	4.55 (8.00)	1.77 (2.29)	2.00 (1.78)
Antimycotics	0	0.09 (0.30)	0	0
Antivirals	0.50 (2.67)	0.91 (2.70)	0.05 (0.21)	0.15 (0.38)
Anti-inflammatories	0.72 (1.45)	1.91 (2.34)	1.50 (2.56)	2.92 (5.14)

Note: Receipt of anti-depressants prescriptions (RAP) in adulthood (age 30–40 years) was defined as having one or more prescription of antidepressants during that time.

depression, continued mental health problems (as indicated by receipt of prescriptions of antidepressants) and the frequencies of anti-infectives and anti-inflammatories prescriptions in adulthood (age 30–40 years). The results indicate that females with a history of adolescent depression received more prescriptions of anti-infectives and anti-inflammatories in adulthood as compared to those without such history. This association was more pronounced in females with a persistent depressive disorder in adolescence and seemed to be mainly driven by those who also were prescribed antidepressants in adulthood. More specifically, persistent depressive disorder followed by an adult condition for which

Table 4
Relationship between adolescent persistent depressive disorder (PDD) in adolescence, receipt of anti-depressants prescriptions (RAP) and prescription of anti-infectives and anti-inflammatories in adulthood (age 30–40 years).

Medication type	Adolescent depression (PDD) & RAP between ages 30 - 40 aIRR (95% CI)	Adolescent depression (PDD), but no RAP between ages 30 - 40 aIRR (95% CI)	No adolescent depression, but RAP between ages 30 - 40 aIRR (95% CI)	No adolescent depression & no RAP between ages 30 - 40 aIRR (95% CI)
Females				
Anti-Infectives	**2.37*** (1.64 – 3.43)**	0.92 (0.61 – 1.38)	1.23 (0.79 – 1.87)	Reference
Antibacterials	**1.97*** (1.38 – 2.79)**	0.97 (0.66 – 1.40)	1.27 (0.85 – 1.87)	Reference
Antimycotics	**6.49*** (2.96 – 14.88)**	2.21 (0.90 – 5.46)	2.22 (0.80 – 5.73)	Reference
Antivirals	2.48 (0.86 – 6.89)	0.27 (0.03 – 1.24)	0.69 (0.13 – 2.47)	Reference
Anti-inflammatories	**3.79*** (2.19 – 6.60)**	1.67 (0.92 – 3.00)	**3.00*** (1.71 – 5.22)**	Reference
Males				
Anti-Infectives	0.47 (0.15 – 1.26)	0.39 (0.14 – 0.98)	1.61 (0.77 – 3.23)	Reference
Antibacterials	0.61 (0.21 – 1.55)	0.56 (0.22 – 1.32)	1.67 (0.81 – 3.38)	Reference
Antimycotics	_	_	_	_
Antivirals	_	_	_	_
Anti-inflammatories	2.94 (0.94 – 9.53)	1.51 (0.47 – 4.89)	2.49 (0.72 – 8.15)	Reference

Note: All analyses were adjusted for age, adolescent chronic somatic disorders, socioeconomic status, and childhood or adolescent anxiety disorders and disruptive behaviour disorder.
Abbreviations: aIRR: adjusted Incidence Rate Ratio; CI, Confidence Interval.
* $p<0.05$.
** $p<0.01$ and.
*** $p<0.001$.

antidepressants were prescribed, was associated with increased anti-infectives prescriptions, indicating a possible vulnerability to infections. This was not the case for females who experienced a persistent depressive disorder in adolescence but were not prescribed antidepressants as adults. Females who were prescribed antidepressants in adulthood had an increased likelihood of receiving anti-inflammatories, regardless of whether they were depressed in adolescence or not. The same pattern of results was not observed in females with episodic depressive disorder and subsyndromal depression, possibly due to the higher rate of psychiatric comorbidity and recurrence of depressive episodes in the PPD group (Jonsson et al., 2011b). The findings in relation to the male population were harder to characterize. However, depressed males with persistent depressive disorder received significantly less anti-infectives prescriptions compared to their non-depressed counterparts. The observation of no consumption of antimycobacterial, immunoglobulins and specific anti-rheumatic agents limits any further remarks concerning those categories of medications.

4.2. Comparison to other studies

These observations confirm and expand on our previous findings from the same cohort (Päären et al., 2012), which showed an increased prescriptions rate in the depressed compared to their non-depressed counterparts between ages 29–31 years. The present study covers a 11-year period, up to age 40, and shows that the observed relationship persists into mid-adulthood. In addition, the present analyses suggest that the observed relationship is amplified by a continued need for treatment with antidepressants in adulthood.

While this study sheds new light on the association of adolescent depression and subsequent use of anti-infectives and anti-inflammatories, the mechanisms are still largely unknown. Our results seem to suggest that the link between early-onset depression and subsequent use of anti-infectives and anti-inflammatories to a large extent could be driven by continued or sustained mental health problems, in this case portrayed by receipt of antidepressants prescriptions. Possible mechanisms involved in this association might include chronic inflammation (Brod et al., 2014) and the immunosuppressive effects of stress hormones (Bauer, 2005; Brod et al., 2014; Zunszain et al., 2011) that have been demonstrated in depression. The susceptibility to infections in depressed individuals has previously been demonstrated in a register-based study with a 17-years follow-up, where a dose response relationship was reported (Andersson et al., 2015). That is, individuals that experienced more episodes of depression tended to have a higher risk of infections compared to those with fewer episodes of depression and those without. This finding is in line with our results, where individuals with adolescent depression and receipt of antidepressants in adulthood were prescribed more anti-infectives. Their results also showed that the vulnerability tends not to be confined to a particular period of time, but rather to persist (Andersson et al., 2015). However, the pathways are likely to be heterogeneous and complex. The behavioural and social circumstances surrounding people with depression could also play a role in the association between adolescent depression and increased susceptibility to infections, for example risky sexual behaviours (Chen et al., 2008; Khan et al., 2009), conflicts in intimate relationships (Jonsson et al., 2011a), smoking, sedentary lifestyle, and poor eating habits (Velten et al., 2014). Some studies also point to antibiotics use as a possible risk factor for depression (Hao et al., 2020; Lurie et al., 2015). It is also possible that a susceptibility to infections precede onset of depression and in turn, these infections act as a risk for the development of depression. Such a bidirectional relationship is consistent with results from previous studies (Euesden et al., 2017; Kostev et al., 2019; Köhler-Forsberg et al., 2019; Leone et al., 2021). However, a recent Swedish population-based cohort study suggesting that severe childhood infections increase the risk of subsequent depression, found that no strong association persisted after adjustment for unmeasured factors shared between family members (Leone et al., 2022). Finally, the reversed associations observed for the male population should be regarded as preliminary findings that must be followed up in future research. Females with early-onset depression have previously been reported to have elevated relative risks of some infections (i.e., gastrointestinal, genitourinary, and respiratory) compared to males (Leone et al., 2021). While the mechanisms behind such sex differences are largely unknown, a tendency of depressed males to seek health care to a lesser extent than females and even their non-depressed counterparts (Möller-Leimkühler, 2000; Parent et al., 2018) may be a contributing factor. At any rate, this is an important signal to both researchers and clinicians to investigate whether the somatic and psychiatric healthcare needs for males with early onset depression are sufficiently met.

4.3. Strengths and limitations

This study used a rich dataset with diagnostically well-characterized subtypes of depression. It also covers medication consumption over a relatively long follow-up period compared to previous studies, enabling us to capture the actual variation in prescriptions in routine practice. However, the study also suffers from some shortcomings. First, no a priori power calculations for the current research questions were done at the initiation of the cohort study in the early 1990s. The proportion of male participants was small, limiting our possibilities to draw firm conclusions about this population. Second, the use of antidepressants prescriptions in adulthood as a proxy measure of continued mental health problems is rather an uncertain approach, as depressive disorders and anxiety disorders often go unrecognized and anti-depressants also have a wide range of indications. In addition, other forms of treatments, including psychological treatment, were not captured. Third, certain medications, especially anti-inflammatories, are also sold as over the counter drugs without a prescription. Therefore, the prescriptions captured in the analysis may underestimate the true consumption. Fourth, the historical and cultural context of this cohort might limit the generalizability of the findings. While the pattern of results presented here may not be a true reflection of the situation for adolescents in Sweden and globally today, as attitudes to mental health and help seeking may have evolved, the general associations between depression and vulnerability to infections might still apply." Fifth, it should be noted that diagnostic interview used at baseline, the DICA-R-A, was based on DSM-III criteria. To conform with current DSM-5 terminology, the DSM-III depression types were converted to DSM-5 terminology. Merging chronic major depressive disorder and dysthymic disorder is consistent with the DSM-5 definition of PDD. However, the criteria for MDD were slightly revised from DSM-III to DSM-5 (most notably, the removal of the bereavement criteria) (Kendler, 2018). Consequently, the DICA-R-A could potentially have resulted in some false negatives when applying DSM-5 criteria. Lastly, the use of prescriptions of anti-infectives and anti-inflammatories as an indicator for incident illnesses is problematic as these medications can be used for several indications. Due to the nature of the available data, we were not able to provide a breakdown in reasons or specific diagnoses for the prescriptions.

4.4. Implications for clinical practice and decision making

Our results add to the growing body of research supporting the urgent need for timely treatment of early-onset depression and coordinated mental and physical healthcare throughout the lifespan. Effective interventions might mitigate the adverse prognosis observed for persistent forms of depression in particular. To recognize comorbid somatic conditions and optimize their treatment at an early stage could be of great clinical relevance, especially since somatic symptoms have been found to predict a worse long-term course (Bekhuis et al., 2016; Bohman et al., 2018). On a general level, the results underscore the need for collaborative and coordinated care for people with early-onset depression. This is in line with recent developments in many countries, where mental health services are increasingly being integrated into primary care (Kroenke and Unutzer, 2017; World Health Organization. Regional Office for Europe, 2015).

5. Conclusion

In females, adolescent depression is associated with increased frequency of antibiotics and anti-inflammatories prescriptions in adulthood. This association is more pronounced in those with persistent depressive disorder, especially the individuals who received antidepressants prescriptions in adulthood. Early coordinated treatment and prevention of recurrences may help alter this adverse course of events.

Author contributions

Conceptualization: RS, IA, AH and UJ. Data curation and formal analysis: RS. Interpretation: IA, AH, HB, AP, A-LvK, LvK, and UJ. Project administration: UJ. Writing—original draft: RS. Writing—review and editing: IA, AH, HB, AP, A-LvK, LvK, and UJ.

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Research data

National regulations regarding data retrieved from the Swedish registries prevent us from sharing any data openly, due to reasons related to confidentiality and protection of human privacy.

Disclosures

The authors declare no conflicts of interest.

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Supplementary materials

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