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Research paper

Duration and timing of depression and risk of family dissolution: A register-based cohort study of newly-formed Danish families

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ABSTRACT

Background: Depression is detrimental to partnership stability. However, it remains unclear if and how the duration and timing of depression affect the risk of family dissolution.
Methods: We conducted a Danish register-based cohort study of newly-formed cohabiting and married couples in 2008 and 2009, who were followed from the second year after family formation. Depressive episodes were defined by individual-level prescription patterns of antidepressant drugs (ATC codes N06A) in either partner. Family dissolution was characterized by the discontinuation of a shared residential address. Using Longitudinal Targeted Minimum Loss-based Estimation, we estimated the risk of family dissolution after 5 years of follow-up under various lengths and timings of depressive episodes.
Results: There were 102,335 families included. The covariate-adjusted risk of family dissolution in families without depressive episodes was 30.0 % (95 % CI 29.6–30.4 %) and 35.5 % (95 % CI 29.5–41.5 %) in families with at least one depressive episode during follow-up. The risk of family dissolution increased with the duration of depressive episodes to 42.2 % (95 % CI 40.8–43.6 %) for five coherent years of depression. Depression shortly after family formation carried higher risk of family dissolution; this risk was 42.3 % (95 % CI 38.4–46.3 %) for depression experienced in the first year of family formation versus 32.9 % (95 % CI 31.8–34.0 %) in the fifth year of family formation.
Limitations: Proxy measures of depression by antidepressant prescriptions fails to identify milder depression. Annual measures of family dissolution precluded more fine-grained analyses of time-intervals.
Conclusions: Depression is disruptive to family stability, particularly with longer duration and early onset after family formation.

1. Background

Mental health is bidirectionally associated with marital transitions through separation and divorce. Social causation proposes that marriage and its dissolution may affect mental health, and social selection proposes that mental health may lead to marital dissolution (Wade and Pevalin, 2004). Among the mental disorders, depression is the leading cause of global health burden (*Lancet Psychiatry*, 2022; *Lancet*, 2020), with a bearing upon the entire lifespan (*Lancet Psychiatry*, 2022). Not surprisingly, depression on its own is bidirectionally linked to marital instability (Bulloch et al., 2009). While it is generally acknowledged that divorce and separation may precipitate depression (Hald et al., 2022; Richards et al., 1997), the dynamics and importance of depression on subsequent familial dissolution is less established. However, findings indicate that depression increase the risk of dissolution (Bulloch et al., 2009; Overbeek et al., 2003; Mojtabai et al., 2017; Christensen et al., 2022; Bünnings et al., 2021), which in turn may be detrimental to well-being, health and financial opportunities for both adults and offspring (Amato, 2000; Auersperg et al., 2019). Therefore, understanding the dynamics of depression and family dissolution is an important step

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towards mitigating harmful effect of the disease. However, research on this topic is hampered by limitations.

Most previous studies are carried out on populations with limited age ranges (Mojtabai et al., 2017; Metsä-Simola et al., 2018), and therefore only few studies generalize to the full population (Christensen et al., 2022; Bünnings et al., 2021). Measures of mental health are oftentimes self-reported and retrospective (Christensen et al., 2022; Bünnings et al., 2021; Breslau et al., 2011; Idstad et al., 2015), which may both inflate measurement imprecision and precipitate recall bias. The majority of studies did not allot focus to individual mental disorders, such as depression, but rather to an overall measure of any psychiatric disorder (Mojtabai et al., 2017; Christensen et al., 2022; Bünnings et al., 2021; Metsä-Simola et al., 2018). Only few studies focused on both partners, despite divorce is not an individual incident (Bünnings et al., 2021; Metsä-Simola et al., 2018). Also, studies have not adequately addressed the impact of timing of onset of the psychiatric disorder to account for resilience of more established relationships. Few studies included both cohabiting and married couples (Bünnings et al., 2021), which is necessary to fully map the full effect of depression on partnership stability, particularly in light of the increasing number of couples who are not married. Furthermore, depression is often treated as a time-bound event (Christensen et al., 2022; Bünnings et al., 2021), but duration of depressive episodes varies substantially (Videbech, 2020; *Reference program for unipolar depression hos voksne*, 2007; Spijker et al., 2002) and, for many, depression is a recurrent condition with episodic presentations of symptoms (Burcusa and Iacono, 2007). Thus, depression ought to be treated as a trajectory of disease. Finally, to understand the role of depression, it is essential to factor in other potential causes of family dissolution (e.g., changes in labor force participation, income, and physical health) that may both be endogenous to depression and affect future depressive state.

In this register-based nationwide cohort study of newly formed families (i.e., cohabiting couples with or without children), we estimate the risk of family dissolution under various lengths and timings of antidepressant use to capture the effect of depression on family dissolution, considering the family as the unit of interest. We applied Longitudinal Targeted Minimum Loss-based Estimation (LTMLE), which permits robust statistical analysis of covariate-adjusted risk differences between exposure groups defined across time.

2. Methods

2.1. Study design and follow-up

We conducted a register-based nationwide cohort study of families who formed in 2008 or 2009 and who had not dissolved by the end of the subsequent years (i.e., 2009 and 2010, respectively). From here on, these families were followed during discrete time-points for up to 5 years or until any family dissolution, emigration or death of either partner. Specifically, at each time-point (in each period, 1 through 5) we characterized an indicator of family dissolution (Y, yes/no) and censoring or death (C, yes/no), an exposure indicator of antidepressant treatment in the preceding year (A, yes/no) as proxy for depression, and a set of time-dependent confounders (L, including the history of antidepressant treatment and baseline covariates) measured up to the exposure period (Fig. 1).

2.2. Data sources

We recorded both family- and individual-level-specific identification numbers (hereafter family and person ID, respectively) from Statistic Denmark's population register, which covers the entire Danish population throughout the study period. From this register, we also included family information indicating family status (e.g., married, cohabiting, and single), date of status change, and other residential information. The family ID was used for linkage to sociodemographic information from the Income Statistics Register, including equivalized disposable income. The person ID enabled inter-register linkage with the following registers; 1) the Civil Registration System (CRS) (Pedersen, 2011; Schmidt et al., 2014), which contains a vast amount of individual-level information including sex, date of birth, vital and migration status, and date of status change; 2) The Danish National Prescription Registry (Kildemoes et al., 2011), which contains individual-level data on all prescription drugs sold in Danish community pharmacies since 1994. Dispensed drugs are recorded according to the Anatomical Therapeutic Chemical classification (ATC) codes; 3) The Danish National Patient Registry (DNPR) (Schmidt et al., 2015), which contains detailed clinical and administrative information on inpatient discharges from 1977, and outpatient and emergency department contacts coverage from 1995. Diagnostic information on primary and auxiliary diagnoses is recorded according to the International Classification of Diseases, eighth revision (ICD-8) until 1 January 1994, and the tenth revision (ICD-10) thereafter; 4) The Psychiatric Central Research Register (Mors et al., 2011), which contains information on psychiatric hospital discharges from 1969, and

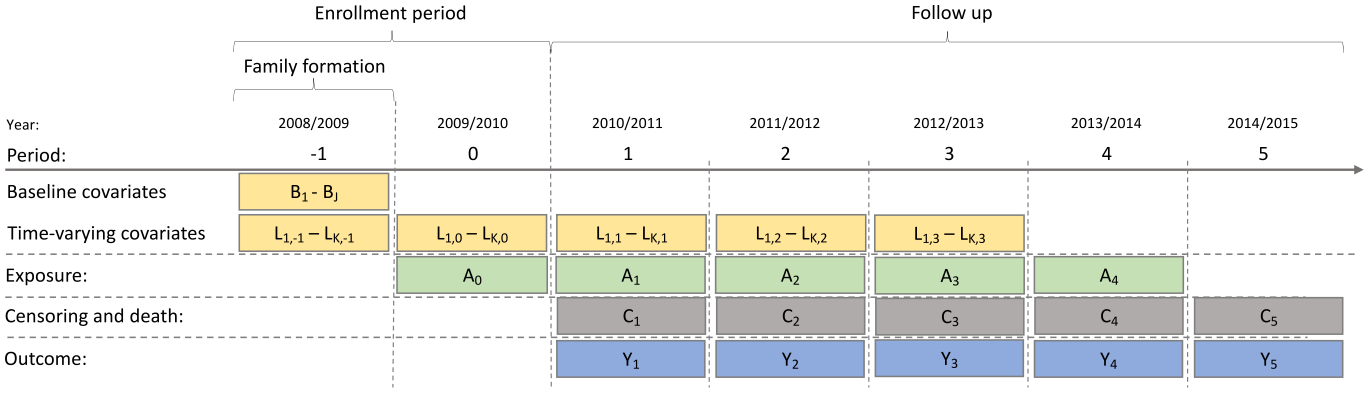

Fig. 1. Schematics of the data structure and variable interrelations.
Families included were formed in 2008 or 2009 and had not dissolved by the end of the subsequent years (i.e., 2009 and 2010, respectively). From the respective anchor year, the families were followed for up during discrete time-points for up to 5 years or until any family dissolution, emigration or death of either partner. At each time-point (in each period, 1 through 5) we characterized an indicator of family dissolution (Y, yes/no) and censoring or death (C, yes/no), an exposure indicator of antidepressant treatment in the preceding year (A, yes/no) as proxy for depression, and a set of time-dependent confounders (L, including the history of antidepressant treatment and baseline covariates) measured up to the exposure period.

outpatient and emergency room contacts from 1995. Psychiatric diagnoses are also recorded according to ICD codes; 5) The Danish Medical Birth Register (Bliddal et al., 2018), which contain medical records of all Danish births since 1973; 6) The Danish Population Education Register (Jensen and Rasmussen, 2011), that contains enrollment and completion dates for any ongoing or completed education.

2.3. Families and study inclusion criteria

We considered newly-formed families as the unit of analysis. We identified all families in 2008 and 2009 by their family ID as two opposite-sex adults (i.e., a heterosexual couple) living together on the same residential address with or without children. To retain only newly-formed families, we excluded families who were also identified by their combined person IDs in the preceding year (i.e., 2007 and 2008, respectively). Remaining families were then classified as married or cohabiting according to Statistic Denmark's characterization of the family; marriage was defined as being legally married, while cohabitation was characterized by a shared residential address and either (i) having shared children, or (ii) if the couple's age difference was <15 years, they were not closely related to each other (siblings or parent-child), and they were the only two adults in the household. Civil status and residential address were allowed to change during follow-up, as long as the couple shared residential address. We included only families in which both couple members were 20 to 60 years of age to, first, reduce risk of misclassification due to versatile living arrangements in early adulthood (e.g., a student renting a room in a house), and, second, to avoid scarcity of families following specific exposure regimes within age strata (i.e., to comply with the positivity assumption). The requirement that families may not dissolve within the first year of formation ensures a minimal and comparable exposure window in each period (i.e., a full year for depression to manifest), and eases compliance with the temporal order of the exposure regimes, the outcome and their confounders.

2.4. Ascertainment of family dissolution

We characterized family dissolution by the discontinuation of a shared residential address for two adults who constituted a family. Such discontinuation is formally identified by a change and discrepancy between each partner's family IDs. These IDs can only be identified at the end of each year due to recording practices, and thus may only be used to make inference about annual events.

2.5. Ascertainment of depression

In Denmark, 85–90 % of medical treatment for depression is initiated in non-hospital settings, while a quarter (26.3 %) received hospital care initially or within five years (Musliner et al., 2019). Thus, to identify depression onset in the full population, we considered redeemed prescriptions of antidepressant drugs as a measure for depression. Namely, throughout follow-up we recorded all redeemed antidepressant drugs (ATC: N06A) (Kildemoes et al., 2011) and created annual indicators (yes/no) of antidepressant treatment, thus constructing longitudinal sequences of indicators used as measures for time-varying trajectories of depression. We characterized hospital-based care for depression according to a registration with a hospital-based diagnosis of single or recurrent depressive episodes (ICD-10: DF32-33) in the current or previous periods (i.e., diagnosed with depression). These measures were then used to define, so-called, dynamic regimes allowing us to examine trajectory specific risks according to temporal ascertainment (any depression within 1 to 5 years of family formation), depression duration (1 to 5 years of consecutive depression), timing of depression (onset of first depression 1 to 5 years after family formation), hospital-based care for depression (ever had hospital-based care or no hospital-based care), the sex of the person suffering from depression (female or male), and the presence of children in the family upon depression onset. Figs. A6–A15 in the appendix display the fraction (in %) of the families following these dynamic regimes during follow-up (years 1 through 5). Using antidepressant drugs as proxy measure for depression has certain limitations, including failure to identify non-drug-recipients whom generally face less severe forms of depression. Antidepressants may also be prescribed for conditions other than depression. We elaborate the potential implications of such constraints in the Discussion section.

2.6. Statistical methods

We applied Longitudinal Targeted Minimum Loss-based Estimation (LTMLE) to estimate the depression trajectory specific risk of family dissolution, accounting correctly for the time-varying nature of exposure groups, permitting robust and data-adaptive adjustment for observed time-varying confounders to produce balanced groups for comparison, and properly handling covariate-dependent right-censoring of survival outcomes (Schomaker et al., 2019; Lendle et al., 2017; Petersen et al., 2014). In this estimation framework, the exposure (depression status) may at any time depend on both past exposure and covariates and affect future exposure and covariates, as well as the outcome. The LTMLE procedure consists of sequential fitting of models for the outcome, censoring, and exposure regime at each point in time, and has desirable analytic and asymptotic properties. Particularly, LTMLE is doubly robust, and provides consistent estimation of the targeted depression trajectory specific risks if either the sequential outcome regression or the treatment and censoring mechanisms are estimated consistently. Standard errors and confidence intervals were calculated from the so-called efficient influence curve. For a more detailed and technical description of the statistical analysis applied in this study, we refer to studies published elsewhere (Lendle et al., 2017; Petersen et al., 2014).

We estimated the risk of family dissolution under the above specified dynamic regimes of antidepressant treatment, taken as estimates of the effect of depression on family dissolution. These longitudinal dynamic regimes allowed summarizing the effects of longitudinal exposure (i.e., the trajectories of depression) on family dissolution. Specifically, we estimated the absolute risk and absolute excess risk of family dissolution according to the duration of depression, the timing of depression, having a hospital contact for depression, according to the sex of the person suffering from depression, and with regards to having children living in the family at depression onset, along with their corresponding confidence limits.

2.7. Sensitivity analyses

Antidepressants may be administered for other purposes than treatment of depression, including other affective disorders and chronic pain. To assess the influence of incorrectly classifying redeemed antidepressants to proxy for depression, we restricted the ascertainment of depression to include only redeemed antidepressants with indication code '0000168' ('mod depression' [against depression]), i.e., we ignored antidepressants redeemed for indications other than depression.

Comorbidity is common in psychiatry, and to assess the risk of falsely attributing any impact of psychiatric co-morbidity to depression, we restricted the analysis to persons without any co-morbid psychiatric disorders (ICD-10: F00-F99).

2.8. Covariates

We include both time-invariant baseline covariates and intermediate time-dependent covariates.

Time-invariant covariates (measured at baseline) were age at family formation of both partners (numerical), (legal) sex (female, male), prior marriage (yes/no), children with previous partnerships (yes/no), and preceding depression (identified using both prescription records and diagnostic information, yes/no). Time-varying covariates measured in

each year of follow-up, included highest completed education (low, medium, high), equivalized disposable income (quintiles), civil status (married or cohabiting), number of joint children (0, 1, 2 or more), psychiatric comorbidity (yes/no), types of antidepressant medication (selective serotonin reuptake inhibitors, serotonin and noradrenalin reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors and other), and somatic co-morbidity as measured by the Nordic Multimorbidity Index (NMI) (Kristensen et al., 2022). We calculated a NMI score for each individual as the sum of the weights for all predictors present before the index year (one and five years for prescriptions and diagnoses, respectively), excluding antidepressants. Finally, we also included an indicator for oral contraceptives (ATC: G03A) (Charlton et al., 2016), which may affect the mood (de Wit et al., 2020), and discontinuation may have critical impact on relationship quality and satisfaction (Russell et al., 2014).

3. Results

There were 102,335 newly formed families included in this study (flow chart available in the appendix Fig. A1). Table 1 depicts the characteristics of the included families from baseline and throughout follow-up. These families consisted of women and men who were on average 32.4 (SD = 9.3) and 34.7 (SD = 9.6) years of age at formation, respectively. During follow-up, 31,845 (31.1 %) of the families dissolved and 5701 (5.6 %) were censored or died. Of the included families, 24,293 (23.7 %) had a depressive episode during follow-up; of these,

Table 1
Population characteristics conditional on periodic survival

Period	Baseline	1	2	3	4	5
Population						
Risk set	102,335	102,335	86,944	78,394	72,459	67,981
Dissolved	–	11,744	19,406	24,658	28,653	31,845
Censoring	–	3647	4535	5218	5701	–
Age						
Women (mean[SD])	32.4 (9.3)					
Men (mean[SD])	34.7 (9.6)					
Depressive episodes						
Antidepressant drugs active		13,390	11,518	10,240	9020	8140
Any antidepressant drugs		13,390	14,161	14,544	14,673	14,642
First antidepressant drugs		13,390	4419	2912	2038	1534
Diagnosis of depression		2747	2386	2180	1997	1836
Psychiatric co-morbidity						
Women		7707	6492	5872	5567	5331
Men		4328	3667	3295	3066	2896
Both		1007	842	746	701	677
Civil status						
Marriage		24,142	28,890	33,017	35,900	38,004
Cohabitation		78,193	58,054	45,377	36,559	29,977
Number of children residing in the family						
0		65,353	46,958	35,402	27,670	22,320
1		26,358	23,440	25,566	24,908	22,590
2 or more		10,624	16,546	17,426	19,881	23,071
Highest level of education in the family						
High		9192	11,469	12,068	12,484	13,009
Medium		19,331	20,466	19,903	19,487	18,884
Low		53,579	45,337	39,044	34,384	30,893
Unspecified		20,233	9672	7379	6104	5195
Disposable income (equivalized)						
1. quintile		22,161	14,352	10,485	9106	9595
2. quintile		20,562	17,331	15,696	14,636	13,923
3. quintile		19,826	18,229	17,058	15,886	14,542
4. quintile		19,851	18,518	17,556	16,414	15,007
5. quintile		19,935	18,514	17,599	16,417	14,914
Nordic multimorbidity index score by sex						
0	Women	62,902	52,629	46,774	43,401	40,535
1	Women	22,031	19,067	17,409	13,843	14,163
2	Women	3712	3303	3022	2774	2950
3	Women	3945	3276	3037	2735	2691
4 or more	Women	9745	8669	8152	9706	7642
0	Men	74,262	62,690	55,682	51,444	48,166
1	Men	13,288	11,142	10,704	9690	8852
2	Men	3928	3549	3223	3091	3072
3	Men	3354	2977	2785	2585	2342
4 or more	Men	7503	6586	6000	5649	5549

16,408 (67.6 %) had two or more consecutive periods with depression, 12,774 (52.6 %) had three or more consecutive periods with depression, 9780 (40.3 %) had four or more consecutive periods of depression, and 3575 (14.7 %) had depression across all five years. During follow-up, 17,433 (17.0 %) of women had a depressive episode compared to 10,178 (9.9 %) men, and in 3318 (13.2 %) of families with depression, both partners suffered depression during follow-up. In the anchor year, 24 % of families were classified as married, 9 % as cohabiting with children, and 67 % as cohabiting without children. Among the families that did not divorce or separate (i.e., remained in the analysis during follow-up), the share of families with higher educational attainment and income, and lower morbidity was higher, indicating that socioeconomically disadvantaged families were more likely to dissolve.

Fig. 2 shows the absolute and excess risk of family dissolution associated with depression according to time since family formation. During follow-up, the covariate-adjusted risk of family dissolution in families without depressive episodes was 30.0 % (95 % CI 29.6–30.4 %) and 35.5 % (95 % CI 29.5–41.5 %) in families exposed to at least one depressive episode during follow-up. In comparison, families with depressive episodes within the first to fourth year of formation led to an absolute excess risk of family dissolution of 12.3 % (95 % CI 8.4–16.3 %) to 6.4 % (95 % CI 0.4–12.3 %), respectively. There was further a clear tendency towards an excess risk of family dissolution associated with any depression episodes within the fifth year of formation, albeit this difference was not statistically significant.

The risk of family dissolution was associated with the duration of depressive episodes (Fig. 3). Prolonged depressive episodes carried greater risk of family dissolution than shorter episodes; compared to no depressive episodes, two and five coherent years of depression carried an absolute excess risk of 7.4 % (95 % CI 2.1–12.7 %) and 12.2 % (95 % CI 10.8–13.6 %), respectively.

The risk of family dissolution was highest when the depressive episodes occurred closely after family formation (Fig. 4). Particularly, depressive episodes within the first year of formation carried an absolute excess risk of family dissolution of 12.3 % (95 % CI 8.4–16.3 %), whereas depressive episodes within five years after family formation carried an absolute excess risk of 2.9 % (95 % CI 1.8–4.0 %).

There was marginally higher risk of family dissolution when men presented with depression as compared to women, but this difference was not statistically significant (Fig. 5).

Compared to families who had not received hospital-based care for depression, those who had carried excess risk of family dissolution (Fig. A2). The absolute risk of family dissolution associated with having received hospital-based care for depression in the first and fifth year after formation was 46.1 % (95 % CI 39.2–52.9 %) and 38.2 % (95 % CI 34.9–42.5 %), respectively.

There were no statistical differences between the depression-induced dissolution risk in families with children or without children regardless of depression ascertainment (Fig. A3). Nonetheless, there was a tendency towards a higher dissolution risk in families without children.

3.1. Sensitivity analyses

Limiting depression ascertainment to include only antidepressant prescriptions with treatment indication ‘against depression’ (compared to any redeemed antidepressant prescription), had only minor impact on the association between depression and subsequent family dissolution (Fig. A4).

Restricting the depression definition to persons without psychiatric comorbidity had negligible impact on the risk of family dissolution; the risk ranged from 43.0 % (95 % CI 39.4–46.6 %) to 34.8 % (95 % CI 29.2–40.4 %) for depression within 1 and 5 years of family formation, respectively (Fig. A5).

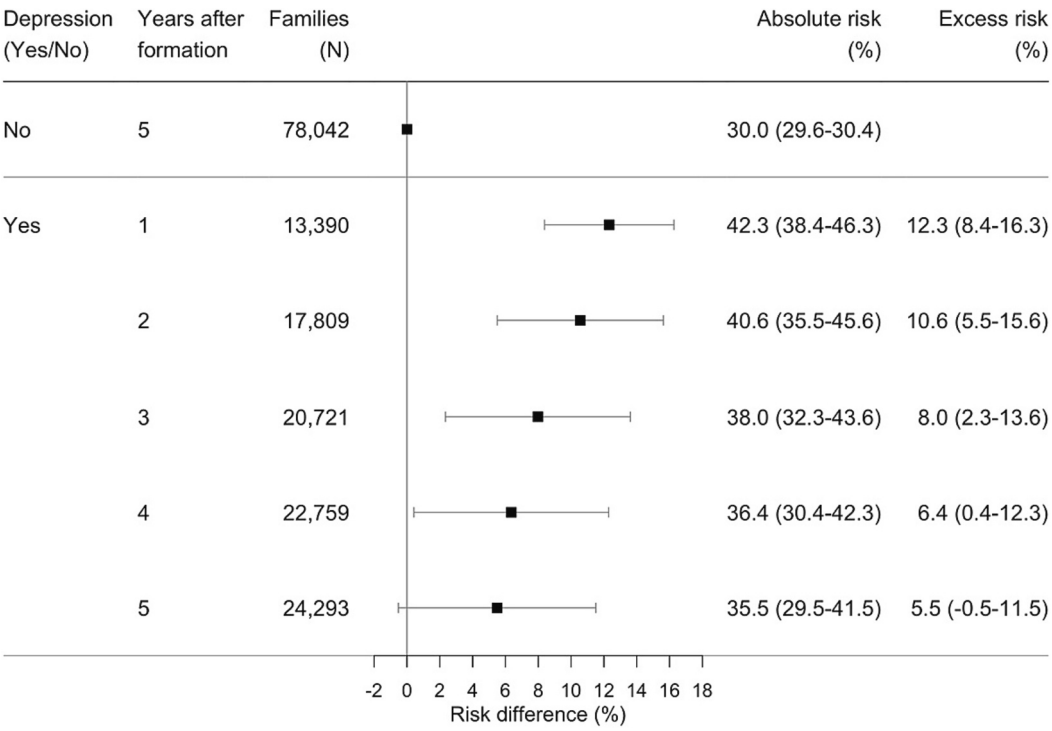

Fig. 2. The absolute risk and absolute excess risk of family dissolution at end of follow-up associated with depression according to years since family formation. *The number of families who had depression at a specific time-point has overlap with the preceding; namely, families who have had depression by the second year of family formation include those who had depression by the first, families who have had depression by the third year of family formation include those who had depression by the first or second, and so on. The dynamic regimes and in extension exact fraction of the population composing the exposure and control groups for each analysis are available in the appendix Fig. A6.

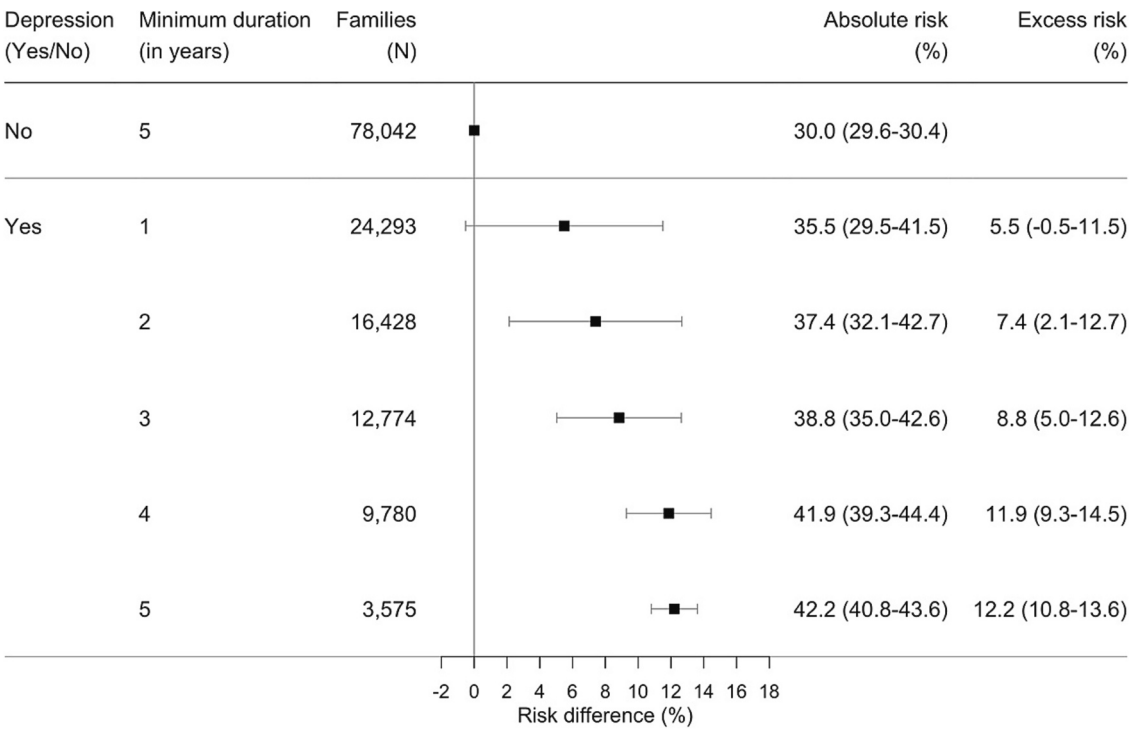

Fig. 3. The absolute risk and absolute excess risk of family dissolution at end of follow-up associated with the duration of depression.
*The number of families who had depression for a specific duration has overlap with shorter; namely, families who have had at least two coherent years with depression also had at least one year of depression, families who have had at least three coherent years with depression also had at least two coherent years of depression, and so on. The dynamic regimes and in extension exact fraction of the population composing the exposure and control groups for each analysis are available in the appendix Fig. A7.

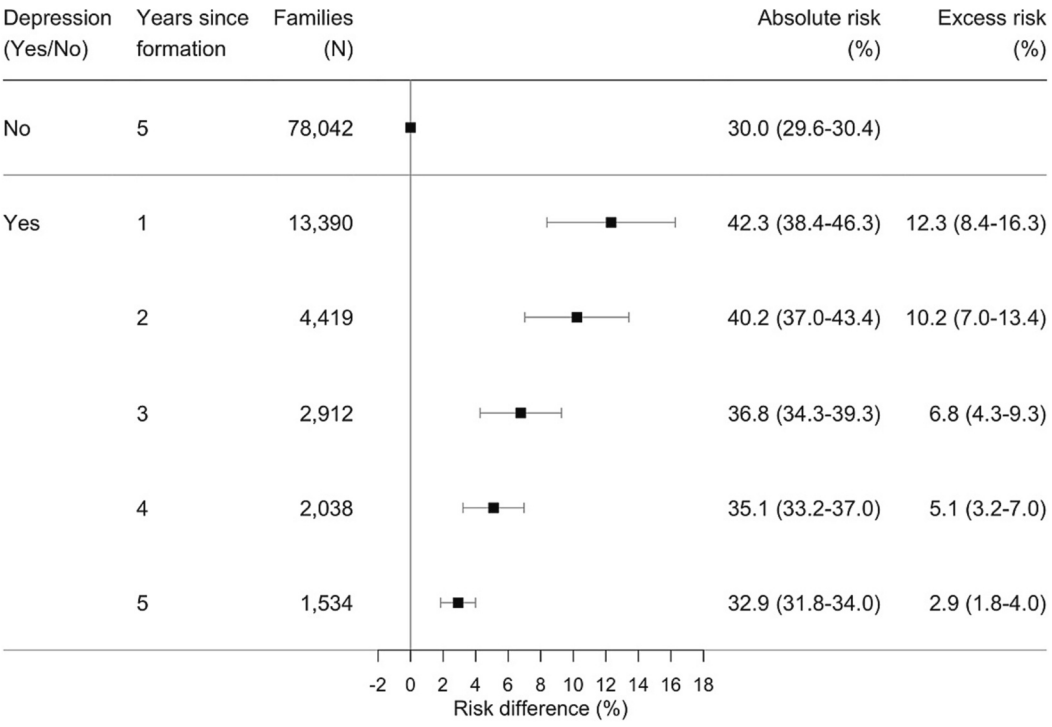

Fig. 4. The absolute risk and absolute excess risk of family dissolution at end of follow-up associated with the timing of depression after family formation.
*The families who had first depression at specific time-points after family formation are disjoint. The dynamic regimes and in extension exact fraction of the population composing the exposure and control groups for each analysis are available in the appendix Fig. A8.

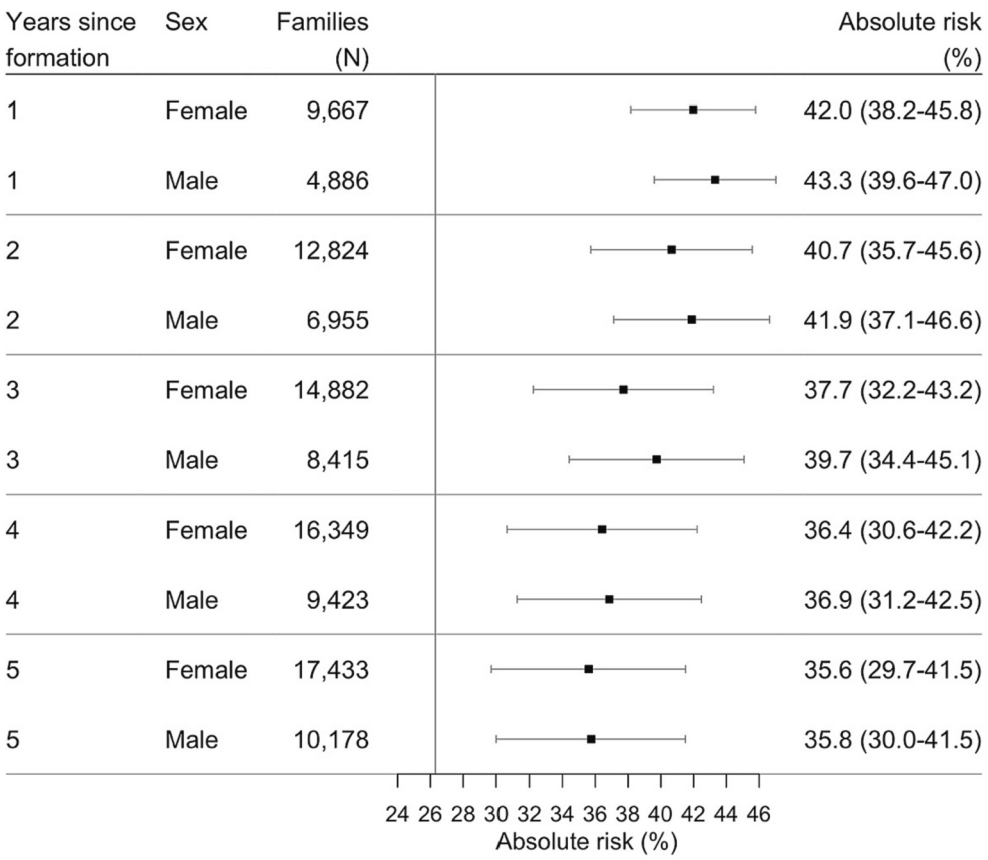

Fig. 5. The absolute risk of family dissolution at end of follow-up associated with the sex of the person affected by depression and time since family formation. *The sex-specific number of families who experienced depression at a specific time-point has overlap with the preceding; e.g., women who have had depression by the second year of family formation include those who had depression by the first, women who have had depression by the third year of family formation include those who had depression by the first or second, and so on. The dynamic regimes and in extension exact fraction of the population composing the exposure and control groups for each analysis are available in the appendix Figs. A12 and A13.

4. Discussion

In this study, we aimed to understand to what extent depression, when considered a course of disease, exerts an effect on family stability. Overall, our results indicate that depression is harmful to relationships and poses a liability to relationship dissolution, particularly with increasing duration of depression, when depression onset presents early after family formation, and when persons received hospital-based care for depression.

In accord with the literature, our results indicated that depression is harmful to relationships and carries risk of familial dissolution (Wade and Pevalin, 2004; Bulloch et al., 2009; Overbeek et al., 2003; Mojtabai et al., 2017; Christensen et al., 2022; Bünnings et al., 2021; Metsä-Simola et al., 2018; Breslau et al., 2011; Idstad et al., 2015). Such dissolution in turn may negatively impact well-being, health and the financial opportunities for adults and their children (Amato, 2000; Auersperg et al., 2019), and calls for depression-specific interventions that may ameliorate conjugal discord. For instance, couple's therapy is known to improve interactional patterns and supportive aspects of relationships, and to be equally effective against depression symptoms as individual psychotherapy while more effective in reducing couples distress level (Barbato et al., 2018). Family psychoeducation may reduce the risk of relapse in persons with depression and may be beneficial for functioning of family relatives, but evidence is mixed (Katsuki et al., 2022).

Our findings clearly suggest that more persistent depressive episodes are increasingly detrimental to relationships. This is consistent with related research on relationship erosion (Coyne et al., 1991; Joosten et al., 2022), in which depressive symptoms interfere with relationship quality by suppressing positive aspects (e.g., support, intimacy) and promoting negative aspect (e.g., conflict), thereby eroding the romantic relationship over time. Even so, our results indicate that presentation of a single depressive episode may still have devastating impact on familial stability. Similarly, Bünnings et al. also conclude that mental health shocks, i.e., a sudden and severe deterioration of mental health, has a negative impact on relationship (Bünnings et al., 2021).

Depression usually lasts from 3 to 12 months, and 10–30 % of patients risk developing chronic depression (i.e., depression lasting two or more years) (Videbech, 2020; *Reference program for unipolar depression hos voksne*, 2007; Spijker et al., 2002). From a nationally representative adult population in the Netherlands, the median and mean duration of depression was 6 and 10.7 months, respectively, and 12 % had not recovered in 36 months (Ten Have et al., 2017). In our study, around 40 % of families with depression were characterized with depressive episodes lasting at least three years, and 14 % were affected in all periods. This is not surprising since the Danish and international recommendations for discontinuation of antidepressant after cessation of depressive symptom are to continue treatment at least 6–9 months after a depressive episode, and two years or longer in the presence of additional risk factors, including previous depressive episodes (Lundsgaard and Videbech, 2020). Thus, treatment of a single depressive episode will often overlap with two years; two years treatment will generally overlap with three years, and so on. Further, our measure of duration mirrors the extent of familial exposure including those where both spouses present with depression (i.e., 13 % of families).

Early depression onset after family formation carried higher risk of

family dissolution than onset at later stages. This may be explained by a lower relationship stability in early adulthood and in the first years after beginning a relationship (Bühler and Orth, 2022). For instance, among married couples, steep declines in marital satisfaction is indeed associated with a higher rate of divorce during the newlywed years, maybe because spouses face fewer barriers to leaving the relationship, or more easily perceive superior alternatives outside of the relationship (seemingly more so for women in the childbearing years) (Lavner and Bradbury, 2010).

Ours and other longitudinal studies (Wade and Pevalin, 2004; Bulloch et al., 2009; Overbeek et al., 2003; Mojtabai et al., 2017; Christensen et al., 2022; Bünnings et al., 2021; Metsä-Simola et al., 2018) build a strong case for the social selection framework i.e., depression often precede family dissolution. However, temporality in the order of events is not sufficient to ensure causality (Hill, 1965; VanderWeele, 2015). The statistical approach taken (i.e., LTMLE) allowed us to quantify effect measures of multiple time-point exposures (here depression) from observational data, and these parameters may be interpreted as causal quantities under certain assumptions (Lendle et al., 2017); namely, the *sequential randomization* and *positivity* assumptions that ensure identifiability (i.e., that we may express to the distribution of exposure-specific counterfactuals by the distribution of the observed data) (Petersen et al., 2014). Sequential randomization means that at each time-point, all common causes of the association of interest are observed and controlled for (i.e., there must not be confounding in *any* period). Positivity means that there must not be scarcity of families who may follow the exposure regimes at any time-point within these confounder strata (Lendle et al., 2017; Petersen et al., 2012).

TMLE offers multiple advantages in our study. One primary benefit is that it makes it possible to study effects of exposures changing over time, such as depression duration or timing of depression onset. Specifically, LTMLE allowed us to gain insights into the time-dependent trends of depression over time, rather than just looking at snapshots of depression status at one point in time. We emphasize that the statistical analysis of such time-varying exposures is only feasible with the tools of modern statistical causal inference like LTMLE. Furthermore, LTMLE is designed to make optimal use of the data, overall improving both the accuracy of predictions and the grounds for a causal interpretation.

In our study, women were more likely to have depression than men, but depression was only marginally more harmful to family stability when the sex of the affected partner was male. Accordingly, research consistently show that women are more likely to be diagnosed with depression than men (Videbech, 2020; Hvidberg et al., 2020; Pedersen et al., 2014). While the reasons for this sex-disparity are likely complex and multifaceted, some factors may be particularly important; among other, hormonal influences (such as during menstruation or pregnancy) or that women are more likely to seek treatment for milder depression. The latter is substantiated by the fact that severe depression is equally common among men and women (*Reference program for unipolar depression hos voksne*, 2007). Hence, the tendency towards higher risk of dissolution in families where men presented with depression may reflect more severe depression. We did not include same-sex couples, and we urge caution with regards to extrapolating these findings to such families.

While people form families for various reasons, and the specific motivations can vary widely over time and between individuals and cultures, one common reason is reproduction and child-rearing (Steffensen, 2017). But children may also bring stressors to the family (Thomas et al., 2017), and having children is associated with higher odds of depression (Giannelis et al., 2021). In particular, postpartum depression is considered to be prevalent in 10–15 % of new mothers and 8–10 % of new fathers (Cameron et al., 2016; Paulson and Bazemore, 2010), and the risk of divorce is more pronounced with severe depression (Johannsen et al., 2021). Further, the risk of recurrent depression is much elevated after postpartum depression (Rasmussen et al., 2017). However, despite that the early postpartum period represents an at-risk period for depression and stress, there were no statistically significant difference in the family dissolution risk between families with and without children associated with depression. If any, there was a signal that having children were to some extent protective against dissolution, although these findings were not statistically significant.

We relied solely on register-based information, thus limiting recall bias from the self-reported and retrospective information previously used in studies of depression (Christensen et al., 2022; Bünnings et al., 2021; Breslau et al., 2011; Idstad et al., 2015). However, we used redeemed antidepressant drugs as proxy measure for depression and there may be misclassification of depression. First, even though as much as 90 % of medical treatment initiation takes place in non-hospital settings (Musliner et al., 2019), for which a person is not registered with a diagnosis, we failed to identify those who received non-pharmacological treatment for depression, and those who sought no treatment at all (*Reference program for unipolar depression hos voksne*, 2007). Correspondingly, in a recent study of agreement between survey and register-based information, 15 % of those with depression in the community was seen in the hospitals (i.e., captured by diagnostic information) while 51 % received medical treatment in a non-hospital setting (i.e., captured by prescription records) (Weye et al., 2023). Hence, using prescription records (as compared to diagnoses) increased our chance of identifying depression in the community. Second, persons with milder depression are less likely to receive treatment, and we are more likely to identify more severe depression (Weye et al., 2023). Jointly, this may lead to inflated measures of the absolute risk of family dissolution in both families with and without depression, but less so for estimates of absolute excess risk and is unlikely to account for the effects of depression found in this study.

Third, antidepressant drugs are prescribed for other conditions that depression (Ishtiak-Ahmed et al., 2022; Forns et al., 2019). Still, in a Danish study of treatment indications for antidepressants in pregnant women, 82 % of the redeemed prescriptions was prescribed for depression, 11 % for anxiety, and 4 % for sleep problems (Liu et al., 2020), suggesting that depression account for far the majority of antidepressants prescribed. In addition, depression and anxiety has substantial shared psychopathology and diagnostic overlap, and meeting criteria for anxiety does not preclude the coexistence of depressive symptoms (Zbozinek et al., 2012). In another study of older adults in Denmark ($\geq$ 65 years of age), 60 % of treatment indications was for depression, 10–15 % for anxiety and sedation, and as much as a third of indication codes was either off-label, missing or unspecified (Ishtiak-Ahmed et al., 2022). Despite such measurement errors, the recorded information of indication in the Danish National Prescription Registry is considered valid and missingness is of minor concern (Harbi and Pottegård, 2024). Accordingly, when restricting to antidepressant prescribed with an indication for depression there were only minor changes to our findings, and we believe our results are not compromised by misclassification.

Premarital cohabitation is very common in Denmark (Svarer, 2019), and close to 75 % of families in our study were classified as cohabitees in the anchor year. A limitation of this study was that the definition of families used precluded identification of same-sex couples without children and consequently we could not consider dissolution among same-sex relationships.

The exact findings presented here reflect the Danish society with high divorce rates, policies and cultural norms that promote economic self-reliance and reduce financial barriers to divorce, making divorce more accessible and socially accepted, and need not extrapolate to other countries with different social norms and attitudes. Despite such limitations to generalizability, we expect the direction of the effect of depression is retained, i.e., that depression remains harmful to partnership stability.

Divorce is also a well-established risk factor for depression (Bulloch et al., 2009; Amato, 2000; Breslau et al., 2011; Bruce and Kim, 1992; Metsä-Simola and Martikainen, 2013; Sbarra et al., 2014; Kendler et al.,

1998), but reversed causation is unlikely to have much influence on our results. First, there was a clear temporal order of measures for depression and family disintegration. Second, treatment-seeking and initiation is often delayed after presentation of depressive symptoms. For instance, in northern European countries, short of half (40–52 %) meeting criteria for depression initiated treatment in the year of onset. Eventually, nearly all (89–99 %) received treatment, but with a median delay of 1–3 years (Wang et al., 2007). Third, chronic stressors (e.g., marital discord) are more highly associated with depression than acute stressors (e.g., divorce) (Kendler et al., 1998).

We have gone great lengths to include a sufficient but not overly rich set of covariates to avoid violating the statistical assumptions, but some important covariates may have been omitted.

For instance, we did not have information about relationship (dis) satisfaction, which predicts divorce, is reciprocally associated with depressive symptoms (Gustavson et al., 2012; Amato and Rogers, 1997; Fincham et al., 1997), and has been shown to reduce the association between women's mental health problems and divorce when adjusted for (Butterworth and Rodgers, 2008). Alcohol and drug abuse is commonly reported as cause for divorce (Amato and Previti, 2003) and is more common among persons with mood disorders than in those without (Metsä-Simola et al., 2018; Boschloo et al., 2011). We included ICD-codes of drug and alcohol abuse, but these presumably capture only little of the variation (albeit maybe the most extreme cases). Parental break-ups and social upbringing may also have a bearing on ones' proclivity to develop depression and stick for better or for worse. There are regional differences in use of antidepressant drugs and divorce rates in Denmark, and we did not include geographic area of residence. However, discrepancies are largely driven by socioeconomic differences, and we may have captured some of the variation.

Persons with more severe depressive symptoms are more likely to receive medical treatment and even more so having referral to the psychiatric hospitals (Weye et al., 2023; Demyttenaere et al., 2004). Families in whom a person received hospital-based care carried higher risk of dissolution than in those whom they did not. Though crude, this sectoral stratification likely revealed how more severe depression on average carried higher risk of family dissolution compared to those milder.

Depression is frequently co-morbid to mental health problems, which may equally put strain on the relationship and precipitate couple's separation and divorce (Christensen et al., 2022; Bünnings et al., 2021; Butterworth and Rodgers, 2008). Including only families with depression (i.e., without psychiatric comorbidity) had only minor impact on the estimated risk of family dissolution, which indicates that depression itself is a driver of relationship instability. However, we did not include prescription of psychopharmacologic agents, and there may be residual confounding.

We did not consider the effect of concurrent depression in both partners because of reduced statistical power, but earlier results indicate that concurrent depression of mental distress in both partners carries higher divorce risk than when only one part were affected (Bünnings et al., 2021; Idstad et al., 2015). However, couple-level spouse similarities in mental distress were to some extent protective again divorce (Idstad et al., 2015), and joint physical health deterioration, if any, seemed to stabilize relationships (Bünnings et al., 2021).

A limitation of our study is that identification of families was based on Statistics Denmark's characterization of families, and we cannot rule out misclassification. For instance, according to this definition we do not capture couples living apart, which may constitute up to 10 % of all couples in some European countries (Liefbroer et al., 2015), and this consequently limits generalizability of our findings. Still, despite recent evolutions in family patterns and normative conceptions of 'family', for the vast majority, moving into a joint household is imperative in the process of union formation (Krapf et al., 2022). Non-conjugal unions of friends may also be misclassified as 'families', albeit limited to the particular setting of two non-related opposite-sex persons with a shared residential address of more than a year. Further, for the majority, partnership dissolution triggers residential moves (Clark, 2013), and we characterized family dissolution according to family ID discrepancies between spouses at the end of each year. However, we may have misclassified temporary transitions in living arrangements as dissolution, if it overlaps two years.

In addition, relying on annual measures on family dissolution precluded more fine-grained temporal division, and we may have missed important acute adverse life events important to dissolution. Namely, to comply with the temporal order of depression and subsequent family dissolution, no information was included on events that occurred in the year of dissolution, including also depression.

We used the years 2009–2010 as anchor years due to their contemporaneity and relevance in providing current data, along with their capacity to afford a sufficiently extensive follow-up duration and data consistency. Still, it is pertinent to acknowledge that several alternative combinations of consecutive years were also considered as viable options.

Differences between types and classes of antidepressants may also inform efforts of family stability. Future studies may want to consider alternate sampling strategies yielding power for such high-resolution analyses.

5. Conclusion

Our results suggest that depression is disruptive to family stability and poses a liability to dissolution, particularly with increasing severity and duration of depression, and with early depression onset after family formation. Further, depression seems equally harmful to families regardless of the sex of the depressed partner.

CRediT authorship contribution statement

Kasper Lolk: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Helene Charlotte Wiese Rytgaard:** Conceptualization, Formal analysis, Methodology, Validation, Visualization, Writing – review & editing. **Malene Galle Madsen:** Investigation, Writing – review & editing. **Gara Arteaga-Henríquez:** Conceptualization, Writing – review & editing. **Kathrine Bang Madsen:** Conceptualization, Investigation, Writing – review & editing. **Julie Werenberg Dreier:** Conceptualization, Formal analysis, Validation, Writing – review & editing. **Trine Munk-Olsen:** Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

Declaration of competing interest

All authors KL, HCWR, MGM, GAH, KBM, JWD and TMO declare no known conflicts of interest that may influence the work reported in this paper. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this paper in consistent with those guidelines.

Data availability

Data were retrieved from Danish national registers and did not require consent from participants. Individual level data supporting the findings in this study are not publicly available due to privacy or ethical restrictions. However, summary statistics, additional results and Supplementary material may be provided on request.

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analysis, nor in the decision to publish or in the preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2024.01.022.

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