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Perception of risk of adverse neurodevelopmental outcomes in offspring related to antidepressant, other psychotropics and mental illness exposure in pregnancy and breastfeeding

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Abstract

Objectives: To investigate (i) women's perceived risk of adverse long-term neurodevelopmental outcomes in offspring following antidepressant, other psychotropics, and mental illness exposure during pregnancy or while breastfeeding, and (ii) factors associated with antidepressant and mental illness risk rating.

Design: Cross-sectional, web-based study.

Setting: Nationwide in Norway, June 2019-June 2020.

Participants: Women of age 18-55 years who were pregnant, recent mothers, or planning a pregnancy, who had been offered antidepressants in the last 5 years.

Primary and secondary outcome measures: Perceived risk of adverse long-term neurodevelopmental outcomes in offspring associated with prenatal and breastmilk exposure to antidepressants, other psychotropic medications, and mental illness itself.

Results: Of the 448 included women, 234 were pregnant, 146 mothers, and 68 were planning a pregnancy. Antidepressants were perceived as least harmful both in pregnancy (mean score 4.2) and breastfeeding (mean score 3.8), relative to antipsychotics, anxiety/sleeping medication, or antiepileptics (mean score range: 6.3-6.5 during pregnancy, 5.6-6.2 while breastfeeding). The perceived risk of mental illness exposure exceeded that of antidepressants (mean score range 5.6-5.9). Factors associated with greater risk perception of antidepressants in both exposure periods among pregnancy planners included lower education level, having a native language other than Norwegian and being job seeker or homemaker (range of β: 1.71-6.3). For pregnant women and mothers, there was an inverse association between the perception of risk in the offspring and perceived effectiveness of the antidepressants in both exposure periods (range of β: -0.28, -0.21).

Conclusions: In a population of women with past/current mental illness, the perceived risk of antidepressant exposure in pregnancy or via breastmilk on child long-term neurodevelopmental outcomes was lower than what was rated for the mental illness itself. Antipsychotics and anxiety/sleeping medication were perceived as most harmful, at par with antiepileptics. Pre-pregnancy counselling should target women with sociodemographic characteristics associated with higher perceived risk.

Article summary

Strengths and limitations of this study

- This is the first nationwide study in Norway about women's perception of child long-term neurodevelopmental risks following psychotropic medication and mental illness exposure during pregnancy and while breastfeeding.
- The perception of risk measures was specific to long-term neurodevelopmental outcomes in offspring.
- The study included only women with a current/past mental illness, who are possible end users of antidepressants and other psychotropic drugs.
- The risk of bias due to self-selection cannot be excluded, although the results were made more generalizable in terms of age and county of residence, using survey weighting.

Introduction

Maternal mental illness occurs in 5-15% of women during the perinatal period, most commonly major depression,[1] anxiety,[2,3] and eating disorders.[4] In addition to the difficulties associated with mental illness for the affected women themselves, these perinatal disorders pose risks for short- and long-term negative outcomes for offspring.[5,6] Women with a perinatal mental illness may therefore be in need of psychotherapeutic or pharmacological treatment, or both, depending on the severity of the condition and therapeutic preference.

Antidepressants, particularly serotonin reuptake inhibitors (SSRIs), are the preferred pharmacological option for the above disorders during pregnancy.[7] Their estimated population prevalence, based on filled prescriptions during pregnancy, is 2.3-3.7%.[8] Other psychotropics, such as benzodiazepines, z-hypnotics and antipsychotics, are less often used.[9,10] Even though multiple studies have shown that antidepressants are not major teratogens,[11–14] findings remain inconsistent about the risk of negative longer-term neurodevelopmental outcomes in children, e.g., autism spectrum disorder.[15,16] Current data about the reproductive safety of antipsychotics and benzodiazepines are limited,[17–19] while the short- and long-term risk posed by the antiseizure drug valproate is now well-acknowledged.[20,21]

In women with a perinatal mental illness, an elevated risk perception of adverse outcomes in offspring due to psychotropic medication exposure often affects the decision-making regarding their treatment.[22–24] The ongoing debate concerning the reproductive safety of these medications may contribute to confusion and decisional conflicts regarding pharmacological treatment, both among women and healthcare providers.[25,26] Several studies have shown that the perceived teratogenic risk of psychotropic medication use may be unrealistically elevated among pregnant women or recent mothers.[24,27,28] In a multinational, web-based study across 18 countries, antidepressants were perceived as almost equally harmful for the developing foetus as alcohol.[28] However, such risk was rated by the general population of pregnant women,

irrespective of their mental illness and current or previous treatment with psychotropics. Understanding the perception of the risk of antidepressants and other psychotropics specifically in women with a mental illness is crucial, as they are possible end users of such medications. Given the uncertainties about the longer-term safety of antidepressants in pregnancy and the high decisional conflicts faced by women considering this treatment,[15,16,29] quantifying the perceived medication risk specifically for long-term neurodevelopmental outcomes in children is clinically relevant.[28]

In a sample of women with current or past mental illness, we aimed to examine the perception of risk of adverse long-term neurodevelopmental outcomes in offspring associated with prenatal and breastmilk exposure to antidepressant and other psychotropic medications, food items and the mental illness itself. To contrast how women rated the perceived risk of antidepressant medication versus that of the mental illness itself, we sought to identify maternal factors associated with how these two risks were perceived.

Methods

Study design and participants

Participants were recruited from the HEALTHx2 study. HEALTHx2 is a cross-sectional, sequential mixed-methods study, in which data was collected from all regions of Norway between June 2020 and June 2021. The quantitative component preceded the qualitative one. The current study used solely quantitative cross-sectional data, which were collected using an electronic questionnaire administered via "Nettskjema" provided by the University of Oslo. Participants could choose to access the questionnaire anonymously or by using their national ID number. Information about the study was posted in multiple pregnancy and motherhood-related websites and apps, in social media, and brochures with the study information were distributed at various psychiatric policlinics, hospital psychiatric departments, and maternity

health clinics (see online Supplement 1, e-only Table 1 for further detail). The complete questionnaire is presented in online Supplement 2. A pilot study was carried out in May 2020, which elicited no major changes to the questionnaire. Women were eligible to participate in the study if they: i) were between the ages of 18-55 years; ii) were planning a pregnancy, were pregnant or had given birth within the last 5 years (hereafter, recent mothers); and iii) have or had previously had a mental illness and been offered antidepressant treatment within the last 5 years.

Ethics statement

This study was carried out in compliance with the Helsinki Declaration. Electronic informed consent was given by the each participant. The Regional Ethics Committee in Norway, region Southeast (reference number 94347), and the Norwegian Centre for Research Data (reference number 943055) approved the study.

Patient and public involvement

The research team attempted to involve patient representatives in the development of the study protocol and the questionnaire, with the support of national mental health patient organisations. No patients could be involved in this study. The national patient organisation for perinatal mental health was consulted for the prioritisation of study aims.

Perception of risk

Participants were asked to rate (from 0 to 10) the perceived harmfulness of substances taken during gestation or while breastfeeding for the long-term neurodevelopment of the child in two separate questions. To enhance reliability, the question specified examples of long-term outcomes in offspring, specifically autism, motor development, language skills, and attention/deficit-hyperactivity disorder. The listed substances included antidepressants,

antipsychotics, anxiety and sleeping medication, antiepileptics (e.g., valproate), mental illness *per se*, cranberries, and alcohol (e.g., wine, beer, spirit). The latter two exposures were listed to act as reference for not harmful and harmful exposures, respectively. Women were asked to tick 'unknown substance' if they had not heard before about the substance. The risk perception measures were adapted from a prior study of perceived risk among pregnant women and new mothers.[28]

Mental health factors

Previous and current mental health was measured via using self-report items in which participants could indicate the mental illness they currently or previously had within a predefined list including: depression, anxiety, obsessive-compulsive disorders, eating disorder, other mental illness, and no mental illness. Participants were also asked to indicate the time points at which they had a mental illness according to their pregnancy status at the time of questionnaire completion. (i.e., planning a pregnancy, currently pregnant or recent mother; see Supplement 1, e-only Table 2). To measure women's mental health burden, we counted the number of different illnesses reported across the available time periods.

Active depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EDPS), a self-rating 10-item scale validated in pregnancy and postpartum for major and minor depression in clinical settings, with satisfactory Cronbach's alpha reliability (0.87).[30] The EDPS has been previously validated in a Norwegian sample.[31] Women were asked to rate whether each item reflected how they had been feeling in the past seven days. Each item response scored 0-3 on an ordinal scale, producing a total EPDS score of 0-30. Higher scores indicate worse symptomatology. A cut-off score of 13 was used to determine the presence of active depressive symptoms.

Current broadly-defined eating disorder subtypes (i.e., anorexia nervosa, bulimia nervosa, binge eating disorder (BED), eating disorder not otherwise specified purging type) were measured via items according to the DSM-IV criteria, by applying an algorithm used in a previous pregnancy cohort study in Norway[4] (see online Supplement 3).

Perceived stigma related to mental illness was measured using four selected items from the "Attitudes Toward Seeking Professional Psychological Help Scale"[32] (ATSPPHS). Participants could indicate the extent to which they agreed or disagreed on each item, with a score ranging from 0 to 4. Scores across items were summed (range 0-20) and a greater score corresponded to more indifference to stigma (i.e., more positive attitudes). This was modelled as a numeric variable. The ATSPPHS was translated to Norwegian and back-translated using two independent translators.

Participants were also asked if they had previously received or were currently receiving psychological therapy (dichotomised as yes/no) and, if yes, the type of therapy and when they received it. Lastly, participants were asked to indicate the perceived effectiveness of antidepressants for treating mental illness both in general and during a pregnancy, by rating this on a scale from 0 ('Not at all') to 10 ('Very useful'). See online Supplement 2 for further details.

Sociodemographic and life-style characteristics

These included women's age, county of residence, number of prior children, marital status, educational attainment and work situation at time of conception (or current for pregnancy planners), body mass index (BMI) at time of conception (or current for pregnancy planners), having Norwegian language as mother tongue, information about future pregnancies (if participants were planning to become pregnant in the near future), the current pregnancy or the latest pregnancy. The questions were based on a prior web-based, cross-sectional study

conducted among pregnant women in Norway.[33] To avoid data sparsity, maternal variables were categorized as shown in Table 1.

Statistical analysis

Descriptive statistics were first conducted and, following this, corrected using survey weight adjustment. The survey weight was based on the most recent data available from the Norwegian Directorate of Health, which describes the proportion of female patients having had contact with psychiatric clinics in each health region of Norway (South-East, West, Middle, North) within each relevant age group (18-29, 30-39, 40-49 years).[34] The weights were calculated by dividing the population proportion by the sample proportion in each age-by-region strata. This implies that the survey weight of underrepresented participants was larger than 1; that of overrepresented participants was smaller than 1. The mean survey weight of the sample 0.7 (range = 0.3-15.4). Data on county was missing for seven participants and the mean weight of the sample were assigned to these. There was no missing data for age. To appraise the impact of confounding by age and region on perception of risk, we also conducted descriptive analyses with no survey weight.

Principal Component Analysis (PCA) was conducted to assess if the risk perception of the various substances could be further grouped; due to the large proportion of women who indicated psychotropic drugs other than antidepressants as 'unknown', the PCA caused substantial data loss. As a result, we focused subsequent analyses on the perceived risk of antidepressant and maternal mental illness exposure only. A pre-registration[35] including the statistical analysis plan is published on the Open Science Framework (some sample statistics had been conducted prior to the publication of this pre-registration, but no analyses related to the outcomes).

Association analyses

To determine which factors were related to the rated risk of antidepressant and maternal mental illness during pregnancy and while breastfeeding, we conducted a series of multiple general linear models with a robust standard error, using the survey weight. These models were built following the 'purposeful selection' approach.[36] Candidate variables were selected based on a p-value < 0.15 in a univariable linear regression model; variables having no role (p-value > 0.05) or yielding a change smaller than 15% in the beta coefficients of the retained variables were removed. We examined a vast array of mental health and sociodemographic factors on risk perceptions. Candidate mental health variables included: current and active depressive symptoms, BED at the time of questionnaire completion, number of self-reported past or current mental illnesses, perceived stigma related to mental illness, psychological therapy, and perceived effectiveness of antidepressant treatment in general and during pregnancy. BED was the sole eating disorder included with sufficient number of women to be included in the association analysis. Candidate demographic variables comprised marital status, work situation, education, having Norwegian as main language, and woman's BMI. Missing data on mental health factors ranged from <1% to 33%, while this issue was minimal (<0.5%) for sociodemographic variables.

The final multiple regression model included statistically significant and clinically relevant factors (i.e., age, education). We replicated the multiple regression model in the three strata of women: planning a pregnancy at the time of questionnaire completion, being pregnant, or recent mothers. Among pregnancy planners, only demographic variables were included due to low sample size. Results are presented as mean difference in risk perception with the corresponding 95% CI, where positive coefficients indicated higher perceived risk and negative coefficients the converse.

Under the assumption that data were missing at random, we imputed incomplete data on the candidate explanatory variables and risk perception of antidepressants and maternal mental

illness via multiple imputation with chained equation (twenty replications). The imputation model included the survey weight, baseline and health-related factors, and auxiliary variables. As sensitivity analysis, we ran mixed-effects models[37] to account for dependence within different regions of Norway (North, South, East and West). The intraclass correlation was below 0.05 in all models, indicating that similarity was low within regions. All statistical analyses were conducted using STATA MP v. 16.

Results

Of the 753 women who indicated their willingness to participate or not in the study, 500 (66% response rate) consented. After excluding participants with missing data for all risk perception substances, age < 18 years, and/or with no self-reported or proxies for current or previous mental illness, we reached a final study sample of 448 women. The data flow to achieve the final study sample is available in online Supplement 4. Background characteristics of the participants are summarised in Table 1. Most participants were either currently pregnant (52%) or recent mothers (33%). The mean gestational week of pregnant participants was 18.5 (SD = 9.8). The majority of recent mothers (61%) had a child between four and twelve months of age. Most planners (59%) were actively trying to conceive at the time of questionnaire response. The overall mean age was 30.8 years (*SD* = 4.6). The majority of women (75%) reported that they have or have had more than two psychiatric illnesses (see Supplement 1, e-only Table 2), and 118 (26%) had active depressive symptoms. Broadly defined BED was observed in 85 (19%) women, and few (<15) were classified as having any other eating disorder type.

Table 1: *Sociodemographic and health-related characteristics of the study sample (N =448)*

	N	%
Sociodemographic characteristics		
Age (years)		
18-29	170	38
30-49	278	62

	N	%
Pregnancy status		
Planning a pregnancy	68	15
Currently pregnant	234	52
Recent mothers (within the last 5 years)	146	32
Geographical health region		
South-East Norway	261	59
West Norway	98	22
Mid Norway	50	11
North Norway	32	7
Marital status		
Married or co-habiting	415	93
Single or divorced/separated	25	6
Other	8	2
Educational attainment (current or at time of conception)		
Primary school	21	5
High school	96	21
University/college	316	71
Other	14	3
Missing	<5	—
Work situation (current or at time of conception)		
Student	32	7
Homemaker	25	6
Health worker (e.g., medical doctor, nurse, pharmacist)	76	17
Other paid work	255	57
Job seeker	14	3
Other	46	10
Norwegian as main language		
Yes	405	91
No	42	9
Missing	<5	—
Health-related characteristics		
Self-reported number of mental illnesses[a]		
One	110	25
Two	172	38
Three or more	166	37
Current symptoms of depression/anxiety		
Yes (EPDS ≥ 13)	118	26
Missing	<5	—
Current broadly defined BED (yes)[b]	85	19
Had received or was currently receiving therapy		
Yes	230	51
No	208	47
Missing	10	2
	Mean	**SD**
Perceived stigma for mental illness[c,d]	9.1	4.1
Perceived effectiveness of antidepressant in general[c,e]	6.9	3.2
Perceived effectiveness of antidepressant in pregnancy[c]	5.3	3.9

Abbreviations: BED=Binge Eating Disorders; EPDS=Edinburgh Postnatal Depression Scale. There was no missing data for pregnancy status, marital status or work situation.
[a]Participants were asked about their history of mental illness; this figure comprise number of psychiatric illnesses from more than one year before to the time of questionnaire completion.
[b]Other EDs were also measured, but had low prevalence in the sample.
[c]Missing data were present for 4 (stigma scale), 7 (health region of residency), 85 (effectiveness of antidepressants in general), and 147 (effectiveness of antidepressants in pregnancy) women.
[d]Greater score corresponds to more indifference to stigma (i.e., more positive attitudes).
[e]Greater score corresponds to higher perceived effectiveness of antidepressants.

As shown in Table 2, cranberry and alcohol were perceived as the least and most harmful substances both in pregnancy and while breastfeeding, respectively. Among the psychotropic drugs, antidepressants were perceived as least harmful both in pregnancy (mean score 4.2) and breastfeeding (mean score 3.8). Participants rated the mental illness itself as somewhat more harmful than antidepressants in both exposure periods (mean scores 5.9 and 5.6). A large number of participants were unfamiliar with the risk of exposure to antipsychotics, anxiety and sleeping medication and antiepileptics. Exposure to most substances was perceived as slightly less harmful in breastfeeding compared with during pregnancy, but the differences were small. The risk perception scores were lower in the survey-weighted analysis relative to the non-weighted (see online Supplement 1, e-only Table 3).

Table 2: *Descriptive statistics of the risk perception scores for seven items in relation to exposure during pregnancy and while breastfeeding*[a]

Substance	Mean risk score (SE)	95% CI	Median risk score	[Q1, Q3]	N	Unknown
Risk perception of exposures during pregnancy						
Alcohol	9.0 (0.1)	[8.8, 9.2]	10	[8, 10]	442	5
Antiepileptics	6.5 (0.4)	[5.7, 7.3]	7	[5. 9]	150	295
Antipsychotics	6.5 (0.3)	[5.9, 7.0]	7	[5, 9]	245	198
Anxiety and sleeping medication	6.3 (0.2)	[5.8, 6.7]	6	[5, 8]	328	116
Maternal mental illness *per se*	5.9 (0.2)	[5.4, 6.3]	6	[4, 8]	423	22
Antidepressants	4.2 (0.3)	[3.6, 4.8]	5	[3, 7]	383	63
Cranberry	0.9 (0.1)	[0.7, 1.1]	0	[0, 1]	301	143
Risk perception of exposures while breastfeeding						
Alcohol	7.1 (0.2)	[6.69, 7.42]	8	[5, 10]	437	9

Substance	Mean risk score (SE)	95% CI	Median risk score	[Q1, Q3]	N	Unknown
Anxiety and sleeping medications	6.2 (0.3)	[5.6, 6.7]	6	[4, 9]	321	124
Antipsychotics	6.1 (0.3)	[5.6, 6.6]	6	[4, 9]	248	198
Maternal mental illness	5.6 (0.3)	[5.0, 6.2]	6	[3, 8]	417	26
Antiepileptics	5.6 (0.4)	[4.9, 6.3]	6	[4, 8]	152	
Antidepressants	3.8 (0.3)	[3.2, 4.4]	4	[2, 6]	376	
Cranberry	1.1 (0.2)	[0.7, 1.6]	0	[0, 1]	298	

[a]These values were corrected by survey weight adjustment. Missing data was < 1.5% for all individual substances. Q1, Q3 indicates the interquartile range.

Figure 1 illustrates the perceived risk in pregnancy (Panel A) or while breastfeeding (Panel B) by pregnancy status (i.e., pregnancy planners, pregnant, or recent mothers). The risk perception was rated similarly by participants with different pregnancy statuses. However, antidepressant and mental illness exposures during pregnancy were perceived as slightly more harmful by pregnancy planners compared with pregnant participants.

Tables 3 and 4 report maternal factors associated with the perceived risks in pregnancy or while breastfeeding, respectively. Having primary school as the highest achieved education level, a native language other than Norwegian, and being a job seeker or homemaker, were the factors most strongly associated with greater antidepressant risk perception in both exposure periods among pregnancy planners (range of β: 2.1-6.3). Health workers rated the risk posed by the maternal illness in both exposure periods significantly higher than women with other paid work (β: 1.77-2.40), but this association was solely present among pregnancy planners.

In both pregnant women and recent mothers, a greater perception of antidepressant effectiveness was associated with a lower risk rating of antidepressants in pregnancy or while breastfeeding, albeit the effect size was small (range of β: -0.21, -0.28). Pregnant women with BED rated the risk of mental illness *per se* significantly higher than the reference group, both for the pregnancy and breastmilk exposure periods (range of β: 1.57-1.70). Mothers who were

unmarried/not cohabiting rated the risk of mental illness exposure in pregnancy significantly lower than the reference group (β: -6.24).

Table 3: *Factors associated with risk perception score for antidepressant and mental illness exposures during pregnancy, by pregnancy status*

	Antidepressants		**Maternal mental illness**	
Maternal predictive factor	*β [95% CI]*	*p-value*	*β [95% CI]*	*p-value*
Planning pregnancy				
Educational attainment				
High school	Ref		Ref	
Primary school	4.14 [2.97, 5.31]	<0.001	1.63 [0.47, 2.79]	0.006
University/college	1.71 [0.47, 2.95]	0.007	N.S.	—
Occupational status				
Other paid work	Ref		Ref	
Homemaker	1.95 [0.65, 3.24]	0.003	N.S.	—
Health worker	N.S.	—	1.77 [0.17, 3.37]	0.030
Job seeker / others	2.50 [0.91, 4.10]	0.002	N.S.	—
Norwegian as native language (No vs. Yes)	3.36 [1.69, 5.04]	<0.001	N.S.	—
Pregnant				
AD effectiveness in pregnancy	-0.26 [-0.41, -0.12]	<0.001	N.S.	—
Psychotherapy (Yes vs. No)	1.11 [-0.00, 2.22]	0.051	N.S.	—
BED (Yes vs. No)	N.S.	—	1.57 [-0.03, 3.18]	0.055
Recent mothers				
Occupational status				
Other paid work	Ref		Ref	
Student	-1.60 [-3.00, -0.19]	0.026	N.S.	—
Homemaker	-1.86 [-3.55, .-0.17]	0.031	N.S.	—
Marital status				
Married or co-habiting	Ref		Ref	
Other	N.S.	—	-6.24 [-6.91, -5.57]	<0.001
Norwegian as native language (No vs. Yes)	2.06 [0.52, 3.60]	0.009	N.S.	—
AD effectiveness in pregnancy	-0.22 [-0.36, -0.07]	0.004	N.S.	—

Notes. Only statistically significant factors are reported. All models were survey-weighted, and adjusted for age and education, in addition to the variables listed in the Table.

Abbreviations: N.S.=non-significant statistically; AD=antidepressant. BED=Binge Eating Disorder.

Table 4: *Predictors of risk perception of antidepressant and mental illness exposures when breastfeeding, by pregnancy status*

	Antidepressants		**Maternal mental illness**	
Maternal predictive factor	*β [95% CI]*	*p-value*	*β [95% CI]*	*p-value*
Planning pregnancy				
Education				
High school	Ref		Ref	
Primary school	6.25 [4.49, 8.01]	<0.001	-2.42 [-4.05, -0.80]	0.003
University/college	1.80 [0.25, 3.35]	0.005	N.S.	—
Other	N.S.	—	4.47 [0.19, 8.76]	0.041
Occupational status				
Other paid work	Ref		Ref	
Homemaker	2.14 [0.72, 3.57]	0.003	-1.95 [-3.29, -.0.62]	0.004
Health worker	N.S.	—	2.41 [0.05, 4.76]	0.046
Job seeker or other	2.56 [0.76, 4.37]	0.005	N.S.	—
Norwegian as native language (No vs. Yes)	3.72 [1.81, 5.63]	<0.001	N.S.	—
Pregnant				
Age				
18-29	Ref		Ref	
30-49	N.S.	—	-1.21 [-2.30, -0.12]	0.030
Education				
High school	Ref		Ref	
Primary school	1.48 [0.24, 2.71]	0.019	N.S.	—
Occupational status				
Other paid work	Ref		Ref	
Job seeker or other	N. S.	—	1.72 [-0.08, 3.52]	0.060
AD effectiveness in pregnancy	-0.21 [-0.36, -0.06]	0.005	N.S.	—
Stigma[a]	-0.16 [-0.30, -0.02]	0.024	-0.20 [-0.33, -0.07]	0.002
BED (Yes vs. No)	N. S.	—	1.70 [0.49, 2.91]	0.006
Recent mothers				
Occupational status				
Other paid work	Ref			
Student	-1.58 [-3.01, -0.16]	.03	N.S.	—
Homemaker	-2.50 [-4.63, -0.37]	.02		
AD effectiveness in pregnancy	-0.28 [-0.43, -0.13]	.00	N.S.	—
Norwegian as native language (No vs. Yes)	N.S.	—	1.34 [-0.04, 2.73]	0.058

Notes. Only statistically significant factors are reported. All models were survey-weighted, and adjusted for age and education, in addition to the variables listed in the Table. Abbreviations: AD=antidepressant; BED=binge eating disorder; N.S.=non-significant statistically.

[a]Perceived stigma related to mental illness was measured using four selected items from the "Attitudes Toward Seeking Professional Psychological Help Scale

Discussion

This study is, to the best of our knowledge, the first to examine the perceived risk of adverse neurodevelopmental outcomes in offspring following exposure to psychotropic drugs and maternal mental illness itself during pregnancy or while breastfeeding. By targeting the evaluation of risk to women who are possible end users of psychotropics, the study generates clinically relevant knowledge about barriers to the decision-making process regarding mental illness treatment in pregnancy or while breastfeeding.

We found that antidepressants were perceived as less harmful than other psychotropic drugs, alcohol, and the maternal mental illness itself, both in pregnancy and when breastfeeding. This is in contrast with a prior study[28] where antidepressants were rated as almost as harmful as alcohol. The perceived risk among participants from Northern Europe in the study by Petersen et al. was also higher than in the current study. There are several possible reasons for these differences. Firstly, there is now greater availability of research data on the longer-term reproductive safety of antidepressants in 2020 compared with 2011, which may have reached the population to a larger degree.[15] Secondly, our study measured the perceived risk for long-term neurodevelopmental outcomes in offspring, whereas prior work[28] focused on structural teratogenic risk. Thirdly, our participants had prior/current mental illness, increasing the likelihood that they would have received tailored counselling on potential risks of antidepressant exposure on the offspring. This could have contributed to a lower assessment of antidepressant risks. This finding is encouraging, as an overestimation of risk may contribute to treatment discontinuation and poor adherence, even when the antidepressant is needed.[38]

A key result is that exposure to mental illness itself in pregnancy and when breastfeeding was perceived as more harmful than antidepressants, and almost at par with other psychotropics. In pregnant women, having BED was associated with greater perceived risk of mental illness exposure in pregnancy and while breastfeeding, relative to women with no BED, which could

be indicative of fears and concerns related to passing on the illness to the child and/or whether maternal eating patterns negatively affect the child.[39] Comparing this finding with prior research is difficult due to lack of similar data. Nevertheless, it points to greater awareness in women about the possible negative consequences of perinatal mental illness for offspring. This finding is important from both a public health and patient-specific perspective.

Confounding by maternal mental illness severity, genetic, and familial environment remains a concern when interpreting the associations between prenatal antidepressant exposure and child development.[15] Maternal perinatal mental illness has been linked to negative health outcomes in the mother, her offspring,[5,40,41] and the family as a whole.[42,43] Negative sequelae include fewer mother-child interactions[44,45] and poorer long-lasting attachment bonds.[46] Therefore, in treating a perinatal mental illness, the potential risks of treatment with psychotropic medication must be balanced against the negative consequences of untreated maternal mental illness for each individual woman. Psychotherapy has moderate effectiveness on postpartum depression,[47,48] and should always be offered as first-line and/or alongside psychotropic medication. Interventions which aim to strengthen social support have also been found to have moderate effects on postpartum depression.[47]

Our observed heightened risk perceptions for antipsychotics and sleeping and anxiety medication in both pregnancy and while breastfeeding may be attributable, at least in part, to the scarcity of research on the longer-term reproductive safety of these medications.[17–19] For many women with psychotic episodes and bipolar disorders, antipsychotics constitute important treatment components.[7] Yet, scarcity of safety data poses serious challenges for clinicians, and women themselves.[49] Even though antidepressants are often taken together with other psychotropics,[38,50] many women in our study were unfamiliar with antipsychotics and sleeping and anxiety drugs, and could not rate their risks.

In line with current recommendations and the available evidence,[20,21] antiepileptics, in specific valproate, were correctly rated as moderately harmful in pregnancy. This greater awareness can be attributable to the nation-wide restrictions on valproate prescribing in fertile women, in force since 2018.[51,52] Other antiepileptic drugs such as lamotrigine, have more favourable safety profile in pregnancy, and their benefit outweigh the risk posed by untreated epilepsy on maternal-child health.[53] Because our questionnaire listed only valproate as drug example for antiepileptics, the observed perceived risk most certainly relates to valproate only, and not to other antiepileptic drugs.

Generally, women did not seem to differentiate between risks of exposure in pregnancy and when breastfeeding to a substantial degree, which is surprising. Clinicians should be aware of this perception, so that they can adequately inform women about the difference in risk during pregnancy or while breastfeeding. Although data on psychotropic excretion into breastmilk and possible effects on the breastfed infant are sparse, most psychotropics are considered compatible with breastfeeding.[53] Breastfeeding is strongly recommended to improve maternal and child health outcomes,[54] and in most cases the benefit of breastfeeding outweighs the potential risks to the infant. However, for specific drugs, e.g., lamotrigine or second-generation antipsychotics, an individual assessment needs to be performed, which includes consideration of infant age, maternal wish to breastfeed, and safer treatment alternatives.[53]

Among pregnancy planners, sociodemographic characteristics such as having primary school as highest education level, native language other than Norwegian, and being unemployed or a homemaker, were associated with increased perceived risk of antidepressant exposure in pregnancy and breastfeeding. Differential access to healthcare and evidence-based counselling, as well as ability to obtain and interpret health information, could in part contribute to these results. These groups of women should be primary targets for preconception intensified counselling. The association between greater perception of antidepressant effectiveness and

lower risk rating of these drugs in pregnancy may point to an increased emphasis on the woman's needs regarding treatment in the perinatal period. Even though the available evidence on antidepressant effectiveness in pregnancy is limited,[55] the psychiatric history of the woman, her response to prior and/or ongoing antidepressant treatment, and outcomes following prior attempts to discontinue the medication, must be part of the individual risk-benefit assessment of antidepressants in pregnancy and while breastfeeding. Such assessment should always be done together with the woman as part of the shared decision-making.

Strengths and limitations

One major strength of our study is that risk perceptions were measured using same methodology as in prior research,[28] with the added advantage of being specific to perceived risk of long-term neurodevelopmental outcomes in offspring. The study had a considerable study size given the difficult-to-reach population, namely women with psychiatric illness around the time of pregnancy, from all regions of Norway. A number of recruitment strategies were implemented to minimize the risk of selection bias. To make the sample more representative, analyses were corrected using survey weight adjustment based on the most recent data from the Norwegian Health Directorate; however this affected our results only minimally.[34] The study used screening tools and diagnostic algorithms validated and/or used in prior research in Norway.[4,31] We also conducted multiple imputation for missing data on both explanatory and outcome variables. The primary analyses of the current study were pre-registered[35], although some sample descriptive statistics had been conducted prior to the pre-registration.

Our study also has limitations. The sample size for women planning a pregnancy was low, and we also suffered some data loss as a large proportion of participants were unfamiliar with antipsychotics, antiepileptics and anxiety and sleeping medication. It is possible that naming branded products could have enhanced recall. The mental illnesses were self-reported by the

participants, and thus dependent on the accuracy of the woman's reporting. However, the eligibility criteria included being offered antidepressant treatment in the last 5 years, thus targeting only moderate to severe mental illness cases. Women with no proxy of current/past mental illness were excluded from the analysis. Use of an electronic questionnaire and multiple recruitment strategies did not permit calculation of a conventional response rate, and bias due to self-selection cannot be ruled out. However, among the women expressing their willingness to participate or not in the study, the response rate was satisfactory (66%). The validity of web-based recruitment methods is now well-acknowledged,[56,57] and the internet penetration rate is almost 100% in women of childbearing age in Norway.[58] Finally, we cannot exclude the possibility that the women who decided to participate in the study differed from the general birthing population of women with mental illnesses in ways that our analysis could not control for.

Conclusion

In a population of women with past/current mental illness, the perceived risk of antidepressant exposure in pregnancy or via breastmilk on long-term neurodevelopmental outcomes in children is lower than what has been previously observed for birth defects. The rated risk of maternal illness exposure exceeded that for antidepressants, which may suggest a growing awareness among women and their healthcare providers of the possible negative sequelae of the illness *per se*. Exposure to antiepileptics, antipsychotics, anxiety and sleeping medication was perceived as most harmful, together with alcohol. Specific sociodemographic variables and perceived effectiveness of antidepressants were significantly associated with rated risk of antidepressants and mental illness, and this knowledge can inform targeted counselling of this patient group. The findings of the current study underline the importance of providing tailored, evidence-based information about the benefits and risks of both psychotropic and mental illness

exposure in pregnancy or while breastfeeding, to facilitate the complex shared decision-making.

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AUTHOR'S CONTRIBUTION: AL conceived the idea for the study; AL, LDB and FT participated in its design and coordination. LDB and AL drafted the manuscript and analyzed the data. AL, LDB, FT, KSH, HKC, KH contributed to the data collection. All authors contributed to the interpretation of the results and revised the manuscript critically for important intellectual content. All the authors read and approved the final manuscript.

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Figure legend

Figure 1: *Perceived Weighted Risk Related to Exposure in Pregnancy (Panel A) and while breastfeeding (Panel B)*

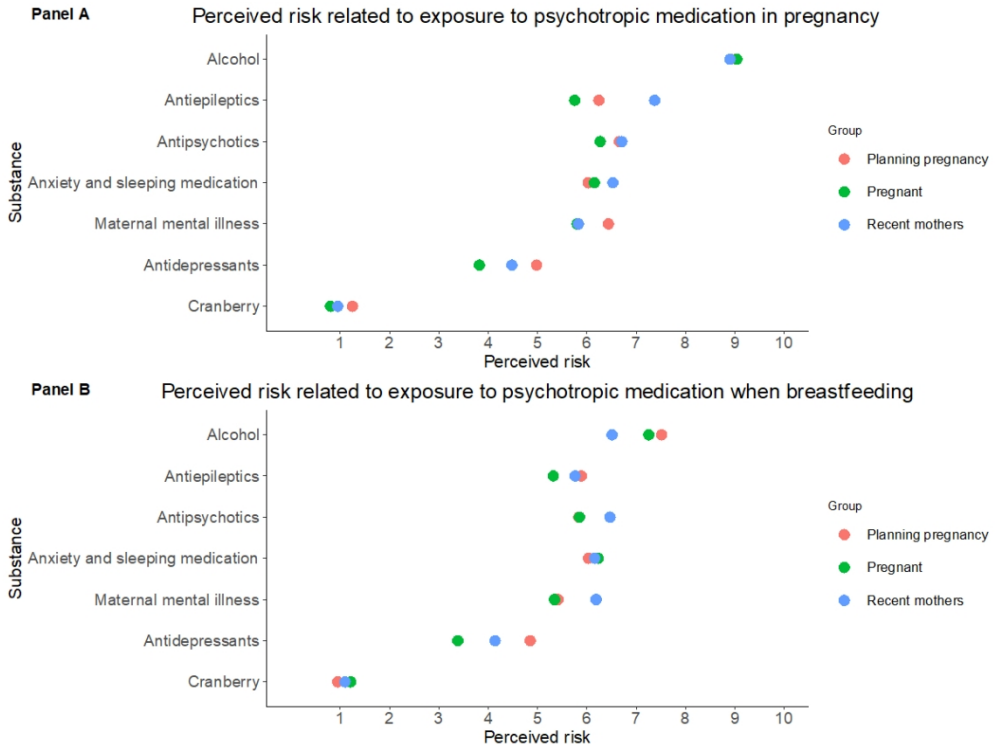


Figure 1: Perceived Weighted Risk Related to Exposure in Pregnancy (Panel A) and while breastfeeding (Panel B)

211x158mm (144 x 144 DPI)

Supplement 1: e-Only tables

e-Only Table 1: Recruitment strategies

e-Only Table 2: Type of reported mental illnesses in women planning a pregnancy (2a), mothers or pregnant (2b)

e-Only Table 3: Descriptive statistics of risk perception, non-weighted

e-Only Table 1: Recruitment strategies used in the study, including psychiatric clinics, websites, apps and social media

Recruitment strategy 1: Informative brochures about the study available at the site, which could be taken freely by the participants	
Site specification/type	*Site location(s)*
Psychiatric outpatient polyclinics	Østre Agder, Lister, Flekkefjord, Solvang, Strømme (Agder region); Lørenskog (Viken region); North of Norway (Tromsø and surrounding areas)
Outpatient polyclinic for anxiety	Flekkefjord (Agder region))
Specialized outpatient polyclinic of psychosomatics and trauma	Lundsiden (Agder region))
Psychiatric hospital ward	Hospital of South Norway (Sørlandet sykehus), Akershus Universitetssykehus HF in Lørenskog (Viken region)
Regional Section for Eating Disorders	Oslo University Hospital, Villa Sult in Oslo
Public prenatal and postnatal care health clinics	Oslo (Grunerløkka district, Østensjø), Stavanger, Bergen, Trondheim, Tromsø, Ås, Tingvoll, Hareid
Recruitment strategy 2: Information about the study on selected pregnancy-motherhood specific websites, as well as medically oriented websites in Norwegian language, social media and pregnancy forums	
General pregnancy / motherhood specific websites or Facebook page	www.ammehjelp.no (breastfeeding support network), www.altformamma.no (general website for mothers),
Medical-specific websites	www.hjelptilhjelp.no (portal for mental health); www.nhi.no (health portal for healthcare personnel and lay persons); www.tryggmammamedisin.no (National medicines information centre for pregnant and breastfeeding women)
Social media	Facebook (featured ads and posts in pregnancy-related and mental health-related pages and groups), Twitter, featured google ads
Pregnancy forums	Kvinneguide (forum for women in general)
Recruitment strategy 3: Information about the study distributed by patient organizations and peers via social media	
Social media	Organization «Psykisk helse» (Mental health) via Twitter; organization "Landsforening1001dager» (perinatal mental health organization) via their Facebook page; "Norske Kvinners Sanitetsforening" (Women association of Norway) via their Facebook and twitter page
Recruitment strategy 4: Information about the study distributed to users of pregnancy-specific or women-specific apps	

Apps	"Clue", an app to track ovulation and pregnancy planning; "Helseoversikt", an app recommended by all prenatal and postnatal health centres in Norway to track health appointments for mother and child, and other health-related information on pregnancy, motherhood and infant care

e-Only Table 2: Type of reported mental illnesses in women planning a pregnancy (2a), mothers or pregnant (2b)

2.a*: Self-reported Mental Illness Among Women Planning to Become Pregnant (N = 68)*[*]

Self-reported illness	More than one year ago	Within the last year	Currently
Depression	24	20	24
Anxiety	15	18	28
OCD	10	2	2
ED	19	4	5
Other mental illness	9	6	11

*Women could report more than one time point for each mental illness.

Abbreviations: OCD=Obsessive-compulsive disorders; ED=Eating Disorders.

2.b: *Self-reported Mental Illness Among Pregnant Women or Recent Mothers (N = 380)*[*]

Self-reported illness	Before pregnancy	During 1st trimester	During 2nd trimester	During 3rd trimester	After birth
Depression	346	84	51	48	101
Anxiety	323	88	64	60	102
OCD	51	10	6	5	17
ED	105	17	9	12	22
Other mental illness	79	20	12	11	26

*Women could report more than one time point for each mental illness.

Abbreviations: OCD=Obsessive-compulsive disorders; ED=Eating Disorders.

e-Only Table 3: Non-weighted mean risk perception of exposures during pregnancy and while breastfeeding

Substance	Mean risk score (SE)	95% CI	Median risk score	[Q1, Q3]	N
Risk perception of exposures during pregnancy					
Alcohol	9.0 (0.18)	[8.8, 9.2]	10	[8, 10]	442
Antipsychotics	6.8 (0.2)	[6.5, 7.2]	7	[5, 9]	245
Antiepileptics	6.6 (0.2)	[6.1, 7.0]	7	[5, 9]	150
Anxiety and sleeping medications	6.4 (0.1)	[6.1, 6.7]	6	[5. 8]	328
Maternal mental illness *per se*	5.8 (0.1)	[5.5, 6.0]	6	[4, 8]	423
Antidepressants	4.7 (0.1)	[4.4, 4.9]	5	[3, 7]	383
Cranberry	1.0 (0.1)	[0.8, 1.2]	0	[0, 1]	301
Risk perception of exposures while breastfeeding					
Alcohol	7.1 (0.2)	[6.8, 7.4]	8	[5, 10]	437
Antipsychotics	6.3 (0.2)	[5.9, 6.6]	6	[4, 9]	248
Anxiety and sleeping medications	6.1 (0.2)	[5.8, 6.4]	6	[4, 9]	321
Antiepileptics	5.9 (0.2)	[5.5, 6.4]	6	[4, 8]	152
Maternal mental illness *per se*	5.6 (0.2)	[5.3, 5.9]	6	[3, 8]	417
Antidepressants	4.3 (0.2)	[4.0, 4.6]	4	[2, 6]	376
Cranberry	1.0 (0.1)	[0.7, 1.2]	0	[0, 1]	298

HEALTHX2 - PATIENT-CENTERED APPROACHES TO AID WOMEN'S DECISION-MAKING AND SET PRIORITIES IN PERINATAL ANTIDEPRESSANT RESEARCH

electronic questionnaire

INFORMATION ABOUT YOURSELF

1. **In which region/province do you live?**
   Region:

2. **Please specify your current pregnancy status**.
   ☐ I am pregnant
   ☐ I have recently given birth (in the last year)
   ☐ I have given birth in the last 5 years

3. (If yes "I am pregnant): **In which pregnancy week are you?**
   From 1 to 44

4. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **How old is your child?**
   ☐ less than 1 month
   ☐ 1-3 months
   ☐ 4-6 months
   ☐ 7-9 months
   ☐ 10-12 months
   ☐ 1-5 years

5. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **Are you currently breastfeeding or have you breastfed your child?**
   ☐ Yes ☐ No

6. (If yes "Are you currently breastfeeding or have you breastfed your child?): **What kind of breastfeeding?**
   ☐ Exclusive with breastmilk from 0 to 4-6 months ☐ Partial with formula/milk from 0 to 4-6 months

7. **Have you been pregnant before? (This also applies to pregnancy that ended in abortion, miscarriage or fetal death)**
   ☐ Yes ☐ No

8. **How many children do you have now?**
   ☐ None ☐ 1 ☐ 2 ☐ more than 2

9. **What is your marital status?**
   ☐ Married ☐ Cohabitant ☐ Single ☐ Divorced/Separated
   ☐ Other/Please specify:_____

10. **What is the highest education you have completed?**
    - ☐ Primary school (10 years of education)
    - ☐ High-school (11-13 years of education)
    - ☐ University / college
    - ☐ Other/Please specify: _____

11. **Your age (in years)?**
From 15 to 55:

12. **Is Norwegian your mother tongue?** ☐ Yes ☐ No

13. **How tall are you (in cm)**?_____

14. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"): **What was your weight at the time of conception (in kg)?** _____

15. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years" or "I am planning a pregnancy"): **What is your current weight now (in kg)?** _____

INFORMATION ABOUT YOUR FUTURE PREGNANCY

(If yes to "I am planning a pregnancy"), for questions 16-19:

16. **When are you planning to get pregnant?**

☐ Within the next 6 months ☐ Within one year ☐ More than 1 year from now

17. **Are you currently trying to conceive?**

☐ Yes ☐ No ☐ Other, please specify_____

18. **Do you smoke cigarettes?**

☐ No ☐ Sometimes ☐ Daily

19. **What is your current work situation?**

☐ Student
☐ Homemaker
☐ Health care personnel, i.e., physician, nurse, or pharmacist
☐ Employed in another sector
☐ Job seeker
☐ None of the above, specify:_____

INFORMATION ABOUT YOUR CURRENT OR LATEST PREGNANCY

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years") for questions 20-23:

20. **Was your pregnancy planned?**

☐ Yes ☐ No, but it was not completely unexpected ☐ No, it was not planned

21. **Did you drink any alcohol after finding out that you were pregnant?**

☐ Yes ☐ No ☐ cannot remember

22. **Did you smoke after finding out you were pregnant?**

☐ No ☐ Sometimes ☐ Daily

23. **What was your work situation when you became pregnant?**

☐ Student
☐ Homemaker
☐ Health care personnel, i.e., physician, nurse, or pharmacist
☐ Employed in another sector
☐ Job seeker
☐ None of the above, specify:_____

HOW YOU ARE DOING AND YOUR MEDICATION USE

The next questions are about your well-being and your use of medication.

24. (If yes to "I am planning a pregnancy"). **Do you have you or have you had any of the following mental illnesses or health problems? If yes, check the box when you have experienced the illnesses.**

	More than 1 year ago	Within the last year	Currently
☐ Depression	☐	☐	☐
☐ Anxiety	☐	☐	☐
☐ Obsessive Compulsive disorder	☐	☐	☐
☐ Eating disorder (for example bulimia, anorexia, binge eating)	☐	☐	☐
☐ Other mental illness	☐	☐	☐
☐ No mental illness	☐	☐	☐

25. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **Have you or have you had any of the following mental illnesses or health problems in the period around your pregnancy? If yes, check the box when you have experienced the illnesses. Please choose the alternatives that apply to you**.

	More than 1 year before pregnancy	1 year or less before pregnancy	In 1st trimester	In 2nd trimester	In 3rd trimester	0 to 6 months after birth	7 to 12 months after birth
☐ Depression	☐	☐	☐	☐	☐	☐	☐
☐ Anxiety	☐	☐	☐	☐	☐	☐	☐
☐ Obsessive Compulsive disorder	☐	☐	☐	☐	☐	☐	☐
☐ Eating disorder (for example bulimia, anorexia, binge eating)	☐	☐	☐	☐	☐	☐	☐

☐ Other mental illness	☐	☐	☐	☐	☐	☐	☐
☐ No mental illness	☐	☐	☐	☐	☐	☐	☐

26. (If yes to "I am planning a pregnancy"). **If you have recently received or receive now psychological treatment (e.g. therapy) for your mental illness, please specify which and when**:

☐ Yes, I receive or have recently received psychological treatment

☐ No, I do not receive or have not recently received any psychological treatment

27. (If yes in question 26). **If yes, what kind? (for example individual psychotherapy, group therapy, counselling session)**_____

28. (If yes in question 26): **If yes, when?**

More than 1 year ago	Within the last year	Currently
☐	☐	☐

29. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **If you have recently received or receive now psychological treatment (e.g. therapy) for your mental illness, please specify which and when**:

☐ Yes, I receive or have recently received psychological treatment

☐ No, I do not receive or have not recently received any psychological treatment

30. (If "Yes in question 29) **If yes, what kind? (for example individual psychotherapy, group therapy, counselling session)**_____

31. (If "Yes in question 29) **If yes, when?**

More than 1 year before pregnancy	1 year or less before pregnancy	In 1st trimester	In 2nd trimester	In 3rd trimester	0 to 6 months after birth	7 to 12 months after birth
☐	☐	☐	☐	☐		

32. **During the past month: have you often been bothered by feelings of sadness, depression or hopelessness?**

☐ Yes ☐ No

33. **During the past month: have you often been bothered by having less interest in things or less pleasure in doing things?**

☐ Yes ☐ No

The next 10 questions are about how you have been doing it for the last 7 days. There are no right or wrong answers. We are only interested in your personal views. (Tick only one box per question)

In this section of the questionnaire - questions 34-43 - ***the Edinburgh Postnatal Depression Scale (EPDS)*** *was presented (Cox J, Holden J, Sagovsky R. Detection of postnatal depression. Development of the 10-item edinburgh postnatal depression scale. The British Journal of Psychiatry. 1987 June 1, 1987;150(6):782-6).*

The next questions are about your weight and weight control.

(If yes to "I am planning a pregnancy"), for questions 44-45

44. **Do you think you are overweight now that you plan a pregnancy?**

- ☐ Yes, a lot
- ☐ Yes, little
- ☐ No

45. **Are you or have you been worried about putting on more weight than necessary during a pregnancy?**

- ☐ Yes, very worried
- ☐ Somewhat worried
- ☐ No, not especially worried

46. (If yes "I am pregnant): **Do you think you were overweight just before this pregnancy?**

- ☐ Yes, a lot
- ☐ Yes, little
- ☐ No

47. (If yes "I am pregnant): **Are you or have you been worried about putting on more weight than necessary during this pregnancy?**

- ☐ Yes, very worried
- ☐ Somewhat worried
- ☐ No, not especially worried

48. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **Do you think you were overweight just in this period:**

	Yes, a lot	Yes, a little	No
Just before the pregnancy	☐	☐	☐
During pregnancy	☐	☐	☐
The first 12 months after birth	☐	☐	☐

49. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **Are you or have you been worried about putting on more weight than necessary in this period:**

	Yes, very worried	Somewhat worried	No, not especially worried
During the last pregnancy	☐	☐	☐
The first 12 months after my latest birth	☐	☐	☐

50. **Has anyone said that you were too thin while you felt that you were overweight during the last 2 years?**
    - ☐ Yes, often
    - ☐ Yes, occasionally
    - ☐ No

(If yes to "I am planning a pregnancy"), for questions 51-52

51. **Have you ever felt that you lost control while eating and were not able to stop before you have eaten far too much?**

	Last 6 months	Currently
No	☐	☐
Infrequently	☐	☐
Yes, at least once a week	☐	☐

52. **Have you used any of the following methods to control your weight during the last 6 months?**

Vomiting	☐ **Atleast once a week**	☐ **Seldom**	☐ **Never**
Laxatives	☐ Atleast once a week	☐ Seldom	☐ Never
Fasting	☐ Atleast once a week	☐ Seldom	☐ Never
Hard physical exercise	☐ Atleast once a week	☐ Seldom	☐ Never

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"), for questions 53-55

53. **Have you ever felt that you lost control while eating and were not able to stop before you have eaten far too much? (remember to choose only the period relevant for you)**

	Last 6 months before this pregnancy	During pregnancy	The first 12 months after birth
No	☐	☐	☐
Infrequently	☐	☐	☐
Yes, at least once a week	☐	☐	☐

54. **Have you used any of the following methods to control your weight during the last 6 months before pregnancy?**

Vomiting	☐ Atleast once a week	☐ Seldom	☐ Never
Laxatives	☐ Atleast once a week	☐ Seldom	☐ Never
Fasting	☐ Atleast once a week	☐ Seldom	☐ Never
Hard physical exercise	☐ Atleast once a week	☐ Seldom	☐ Never

55. **Have you used any of the following methods to control your weight during pregnancy?**

Vomiting	☐ Atleast once a week	☐ Seldom	☐ Never
Laxatives	☐ Atleast once a week	☐ Seldom	☐ Never
Fasting	☐ Atleast once a week	☐ Seldom	☐ Never
Hard physical exercise	☐ Atleast once a week	☐ Seldom	☐ Never

(If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"):

56. **Have you used any of the following methods to control your weight during the first 12 months after pregnancy?**

Vomiting	☐ Atleast once a week	☐ Seldom	☐ Never
Laxatives	☐ Atleast once a week	☐ Seldom	☐ Never
Fasting	☐ Atleast once a week	☐ Seldom	☐ Never
Hard physical exercise	☐ Atleast once a week	☐ Seldom	☐ Never

57. **Is it important for your self-image that you maintain a certain weight?**

☐ Yes, very important
☐ Yes, quite important
☐ No, not especially important

The next questions are about your views about use of antidepressant medication during pregnancy.

58. **Have you previously taken or are you currently taking antidepressant medications?**

☐ Yes, I have previously taken and/or I am currently taking antidepressant medication
☐ No

59. **What is your preference regarding treatment with antidepressant during pregnancy?**

☐ Continue treatment with the same antidepressant(s)
☐ Switch to another antidepressant
☐ Discontinue use of the antidepressant
☐ Reduce the dose of the antidepressant
☐ No preference
☐ Other, specify:_____

60. **Do you think that antidepressants can be safely used in all phases of pregnancy? (You can choose multiple answers)**

☐ No
☐ A woman should receive tailored counselling to facilitate her decision-making whether to take medications or not
☐ Use has to be stopped because it is harmful to the unborn child
☐ Use must not be discontinued, because this can be harmful for maternal mental health
☐ No preference
☐ Other, specify:_____

61. (If yes to "I am planning a pregnancy"). **The next questions are about your treatment with antidepressant medication. If you are taking now or have taken antidepressant medication for your mental illness in the last 6 months, please select the relevant antidepressants from the list below and when you used them. If you did not take antidepressant, you can skip this question**.

	Last 6 months	Now
☐ Fluoxetine (incl. Fontex, etc)	☐	☐
☐ Fluoxetine (incl. Fluoxetin Mylan, Fluoxetine Orion, Fontex)	☐	☐
☐ Citalopram (incl. Cipramil Farmagon, Cipramil Lundbeck, Citalopram Sandoz)	☐	☐
☐ Escitalopram (incl. Cipralex Farmagon, Cipralex Lundbeck, Escitalopram Actavis)	☐	☐
☐ Paroxetine (incl. Seroxat, Paroxetin Actavis, Paroxetin Farmagon)	☐	☐
☐ Sertraline (incl. Sertralin HEXAL, Zoloft, Sertraline Accord)	☐	☐
☐ Fluvoxamine (incl. Fevarin Mylan, Fevarin Orifarm)	☐	☐
☐ Venlafaxine (incl. Efexor, Venorion, Venlazid, Venlafaxin Bluefish)	☐	☐
☐ Duloxetine (incl. Cymbalta, Duloxetin Pensa, Duloxetine Mylan)	☐	☐
☐ Mirtazapine (incl. Remeron, Mirtazapin Bluefish)	☐	☐
☐ Reboxetine (incl. Edronax)	☐	☐
☐ Mianserin (incl. Mianserin Mylan, Tolvon)	☐	☐
☐ Amitriptyline (incl. Anafranil, Klomipramin Mylan)	☐	☐
☐ Clomipramine (incl. Anafranil, Klomipramin Mylan)	☐	☐
☐ Trimipramine (incl. Surmontil)	☐	☐
☐ Nortriptyline (incl. Noritren)	☐	☐
☐ Doxepine (inkl. Sinequan)		

62. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **The next questions are about your treatment with antidepressant medication. If you are taking now or have taken antidepressant medication for your mental illness in the period around pregnancy, please select the relevant antidepressants from the list below and when you used them. (Remember to choose relevant alternatives). If you did not take antidepressant, you can skip this question**.

	More than 6 months before pregnancy	6 months or less before pregnancy	1st trimester	2nd trimester	3rd trimester	0 to 6 months after birth	7 to 12 months after birth
☐ Fluoxetine (incl. Fluoxetin Mylan, Fluoxetine Orion, Fontex)	☐	☐	☐	☐	☐	☐	☐
☐ Citalopram (incl. Cipramil Farmagon, Cipramil Lundbeck, Citalopram Sandoz)	☐	☐	☐	☐	☐	☐	☐
☐ Escitalopram (incl. Cipralex Farmagon, Cipralex Lundbeck, Escitalopram Actavis)	☐	☐	☐	☐	☐	☐	☐
☐ Paroxetine (incl. Seroxat, Paroxetin Actavis, Paroxetin Farmagon)	☐	☐	☐	☐	☐	☐	☐
☐ Sertraline (incl. Sertralin HEXAL, Zoloft, Sertraline Accord)	☐	☐	☐	☐	☐	☐	☐
☐ Fluvoxamine (incl. Fevarin Mylan, Fevarin Orifarm)	☐	☐	☐	☐	☐	☐	☐
☐ Venlafaxine (incl. Efexor, Venorion, Venlazid,	☐	☐	☐	☐	☐	☐	☐

	More than 6 months before pregnancy	6 months or less before pregnancy	1st trimester	2nd trimester	3rd trimester	0 to 6 months after birth	7 to 12 months after birth
Venlafaxin Bluefish)							
☐ Duloxetine (incl. Cymbalta, Duloxetin Pensa, Duloxetine Mylan)	☐	☐	☐	☐	☐	☐	☐
☐ Mirtazapine (incl. Remeron, Mirtazapin Bluefish)	☐	☐	☐	☐	☐	☐	☐
☐ Reboxetine (incl. Edronax)	☐	☐	☐	☐	☐	☐	☐
☐ Mianserin (incl. Mianserin Mylan, Tolvon)	☐	☐	☐	☐	☐	☐	☐
☐ Amitriptyline (incl. Anafranil, Klomipramin Mylan)	☐	☐	☐	☐	☐	☐	☐
☐ Clomipramine (incl. Anafranil, Klomipramin Mylan)	☐	☐	☐	☐	☐	☐	☐
☐ Trimipramine (incl. Surmontil)	☐	☐	☐	☐	☐	☐	☐
☐ Nortriptyline (incl. Noritren)	☐	☐	☐	☐	☐	☐	☐
☐ Doxepine (inkl. Sinequan)	☐	☐	☐	☐	☐	☐	☐

63. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **Did you take antidepressant medications for your mental illness while breastfeeding?**

☐ No, never
☐ Yes, but the child received pumped milk when I took the medication(s)
☐ Yes, irrespective of the use of antidepressant(s)
☐ Yes, but I adapted the timing for breastfeeding according to the intake of the antidepressant
☐ Cannot remember

☐ Other, specify:_____

64. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **Have you purposely stopped taking your prescribed antidepressant(s) during pregnancy?**

☐ Yes ☐ No ☐ Cannot remember

65. (If yes in question 64) **Which antidepressant(s) was it?**

_____

66. If yes in question 64) **Who recommended you to avoid antidepressant in pregnancy?**

☐ Physician
☐ Midwife
☐ Pharmacy personnel
☐ Family/friends
☐ Internet
☐ Nobody, my own initiative

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years").

67. **Was the dose of your prescribed antidepressant changed during pregnancy?**

☐ Yes, increased
☐ Yes, reduced
☐ I stopped taking the medication
☐ No

68. (If yes to "I am planning a pregnancy"): **On a scale from 0 (not at all) to 10 (very effective), how effective do you think your therapy with antidepressants is in treating your illness in general?**

0 1 2 3 4 5 6 7 8 9 10

69. If yes to "I am planning a pregnancy"): **On a scale from 0 (not at all) to 10 (very effective), how effective do you think your therapy with antidepressants will be in treating your illness during a future pregnancy?**

0 1 2 3 4 5 6 7 8 9 10

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years").

70. **On a scale from 0 (not at all) to 10 (very effective), how effective do you think your therapy with antidepressants is in treating your illness in general, regardless of your current or latest pregnancy?**

0 1 2 3 4 5 6 7 8 9 10

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years").

71. **On a scale from 0 (not at all) to 10 (very effective), how effective do you think your therapy with antidepressants was/is in treating your illness during your latest or current pregnancy?**

0 1 2 3 4 5 6 7 8 9 10

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years").

72. **If you are taking or have been taking other medications than antidepressants for your mental illness during the period of pregnancy, please choose relevant medications from the list below, and when you were using them.**

	6 months or less before pregnancy	1st trimester	2nd trimester	3rd trimester	After birth
Paracetamol (for example Panodil, Pinex)					
Opioid analgesics (for example Paralgin forte, Tramadol)					
Lithium (Lithionit)					
Antipsychotics (for example Zyprexa, Seroquel)					
Anxiolytics (for example Valium, Sobril, Atarax)					
Sleeping medications (for example Imovane, Stilnoct, Zolpidem)					

YOUR DECISION-MAKING ABOUT ANTIDEPRESSANT TREATMENT

The next questions are about your decision-making difficulties related to use of antidepressants in the period around pregnancy. There are no right or wrong answers. We are only interested in your personal views.

73. If yes to "I am planning a pregnancy"): **Which treatment option would you prefer during a future pregnancy?**

- ☐ Pharmacological treatment with antidepressants
- ☐ Non-pharmacological treatment
- ☐ Combined non-pharmacological with antidepressants & therapy
- ☐ No treatment
- ☐ Unsure

74. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **Which treatment option do you prefer in pregnancy?**

- ☐ Pharmacological treatment with antidepressants
- ☐ Non-pharmacological treatment
- ☐ Combined non-pharmacological with antidepressants & therapy
- ☐ No treatment
- ☐ Unsure

(Applicable to both questions 73 and 74): *In this section of the questionnaire,* ***the Decisional Conflict Scale (DCS)*** *was presented (O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30).*

YOUR PERCEPTION OF RISK DURING PREGNANCY AND WHILE BREASTFEEDING

75. Below is a list with various medications, food and other substances. Please indicate how harmful you think they are during pregnancy and lactation on a scale from 0 to 10, where 0 corresponds to 'not harmful' and 10 to 'very harmful'. With the word "harmful", we mean in relation to child longer-term development (for example autism, motor or language development, ADHD).

	Unknown substance	0	1	2	3	4	5	6	7	8	9	10
How dangerous are these during pregnancy for your child development?	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antidepressants	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antipsychotics	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Anxiolytic benzodiazepines and sleeping drugs	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antiepileptics (e.g., valproate)												
Cranberry	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Maternal psychiatric disorder	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Alcohol (*e.g. wine, beer, spirits*)	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
How dangerous are these while breastfeeding for your child development?	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antidepressants	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antipsychotics	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Anxiolytic benzodiazepines and sleeping drugs	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antiepileptics (e.g., valproate)												
Cranberry	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Maternal psychiatric disorder	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Alcohol (*e.g. wine, beer, spirits*)	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦

If you have not heard before about such substance, tick 'unknown substance'.

YOUR RELATIONSHIP TO YOUR DOCTOR AND TO YOUR PARTNER DURING PREGNANCY AND YOUR ATTITUDES TO MENTAL DISORDERS

Finally, here are some questions about your relationship with your doctor and your partner, as well as your attitudes towards mental illness. There are no right or wrong answers. We are only interested in your personal views. (Tick only one cross for each line)

a) **Your relationship with your doctor and your partner:**

In this section of the questionnaire, selected items of the "**Antidepressant Compliance Questionnaire" (ACQ)** tool were presented (K. Demyttenaere, et al. Development of an antidepressant compliance questionnaire. Acta Psychiatrica Scandinavica, 2004: 110; 3. 201-207).

b) **Your attitudes towards mental disorders:**

In this section of the questionnaire, selected items of the "**Indifference to stigma"** subscale were presented (Mackenzie et al. *An Adaptation and Extension of the Attitudes Toward Seeking Professional Psychological Help*. Journal of Applied Social Psychology. *2006:* 34; 11. 2410-2433).

Thank you for your help!

Supplement 3: Additional details on Methods

Self-reported psychiatric illnesses

Overall, 10 participants planning the pregnancy did not report any psychiatric illness, and left blank the section "no mental illness". Two of these were classified as having binge eating disorder based on the DSM-IV algorithm, and were thus treated as having an eating disorder. Four reported feelings of low mood in the last month and were therefore treated as having depression. One had a history of antidepressant use and was treated as having 'other mental illness'. Three participants with pregnancy status 'planning' were excluded due to their incomplete self-report item for psychiatric illness and no proxy that could be used.

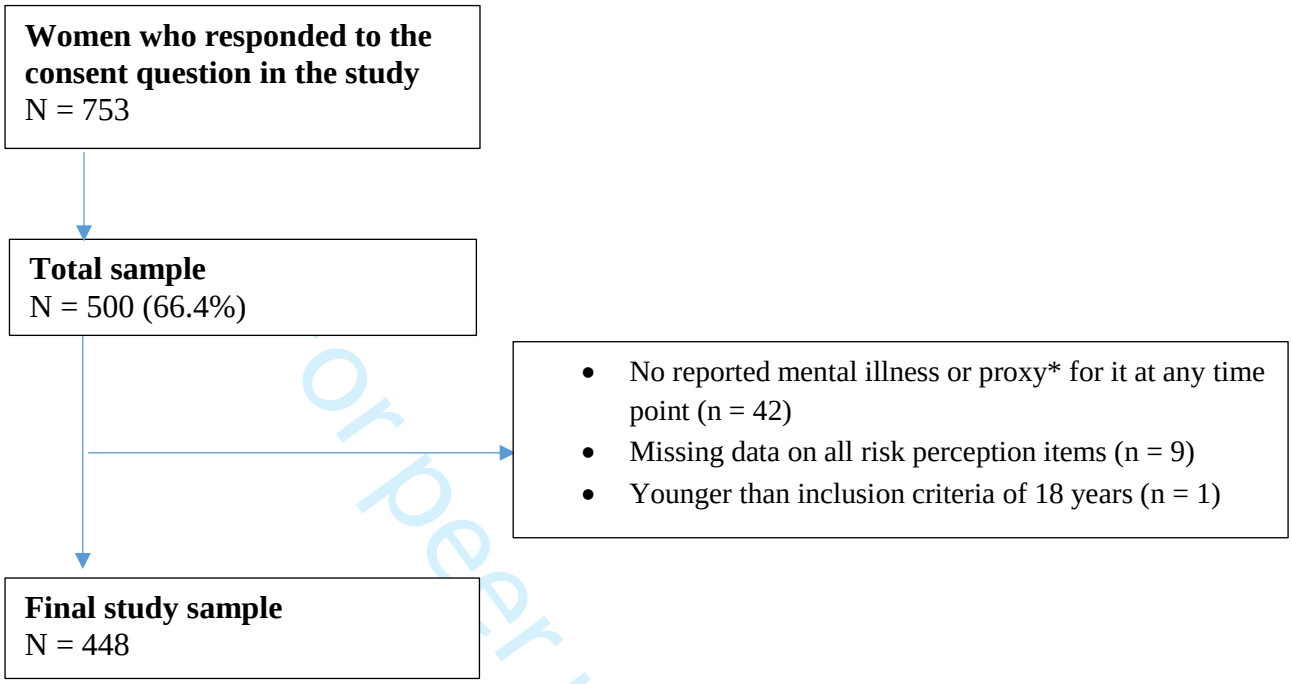
Of the participants who were pregnant or recent mothers, 49 had not completed the item for self-reporting psychiatric illness. One participant had active depressive symptoms based on the EPDS score higher than 13, and was treated as having depression. Seven participants reported having experienced low mood in the last month and were treated as having depression. Three participants had reported having lost interest or low pleasure from doing things and were treated as having had or having depression.

Procedure for the eating disorder classification

Eating disorders (EDs) were classified using an algorithm used by Bulik et al. (2007), for which diagnoses aligned with the DSM-IV diagnostic criteria. This included several eating disorder subtypes. Broadly defined anorexia nervosa (AN) was defined as meeting all DSM-IV AN criteria, except for amenorrhea, and a BMI below 18.5. Broadly defined bulimia nervosa (BN) was defined as endorsing at least weekly frequency of binge eating and purging. BN any type included either purging or binge eating, BN purging type included those who were only purging, and BN non-purging type included only non-purging. Broadly defined binge eating disorder (BED) was defined as at least weekly frequency of binge eating, but with no compensatory behaviours occurring. Eating disorder not otherwise specified, purging type (EDNOS-P) was defined as purging at least weekly, but with no binge eating occurring.

Supplement 4: E-only figures

e-Only Figure 1: Data flow to achieve the final study sample



*Proxies of mental illness included having used a psychotropic medication or non-pharmacological psychotherapy in the past or currently, having an eating disorder according to the DSM-IV algorithm, having active depressive symptoms or self-harm thoughts at the time of questionnaire response as measured by the EPDS scale, or the PHQ2 scale. These proxies were used to verify whether women with missing or no reported mental illness based on self-reported diagnoses, had proxies of mental illness (since this was an eligibility criterion in the study).

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Perceived risk of adverse neurodevelopmental outcomes in offspring related to psychotropics and mental illness exposure in pregnancy and breastfeeding: a cross-sectional survey of women with past or current mental illness

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Perceived risk of adverse neurodevelopmental outcomes in offspring related to psychotropics and mental illness exposure in pregnancy and breastfeeding: a cross-sectional survey of women with past or current mental illness

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Abstract

Objectives: To investigate the perceived risk of psychotropics and mental illness exposure (1) during pregnancy or (2) while breastfeeding on offspring neurodevelopment, and factors associated with this perception in women with past/current mental illness.

Design: Cross-sectional, web-based study.

Setting: Nationwide in Norway, June 2019-June 2020.

Participants: Women aged 18-55 years who were pregnant, recent mothers, or planning a pregnancy, and had been offered antidepressants in the last 5 years.

Primary and secondary outcome measures: Perceived risk of prenatal and breastmilk exposure to psychotropic medications and maternal mental illness on offspring neurodevelopmental outcomes.

Results: We included 448 women: 234 pregnant, 146 mothers, and 68 planning a pregnancy. On a 0-10 scale, women perceived antidepressants as least harmful both (1) in pregnancy (mean score 4.2, 95% CI: 3.6, 4.8) and (2) while breastfeeding (mean score 3.8, 95% CI: 3.3, 4.4), relative to antipsychotics, anxiety/sleeping medication, or antiepileptics (mean score range: 6.3-6.5 during pregnancy, 5.5-6.2 while breastfeeding). Many participants were unfamiliar with psychotropics other than antidepressants. The perceived risk of mental illness exposure exceeded that of antidepressants (mean score range 5.6-5.9) in both exposure periods. Using general linear models, factors associated with greater antidepressant risk perception in both exposure periods included having lower education, non-Norwegian native language, and employment status (range mean score difference (β): 2.07-6.07). For pregnant women and mothers, there was an inverse association between perceived risk and the perceived antidepressant effectiveness in both exposure periods (range of β: -0.18, -0.25).

Conclusions: In women with past/current mental illness, the perceived risk of antidepressant exposure on child neurodevelopment was lower than that for maternal mental illness. Other psychotropic medications were perceived as more harmful. As medication risk perception influences the decision-making regarding treatment of mental illness, pre- and pregnancy counselling should target women with characteristics associated with higher perceived risk.

Article summary

Strengths and limitations of this study

- This is the first nationwide study in Norway about women's perception of child long-term neurodevelopmental risks following psychotropic medication and mental illness exposure during pregnancy and while breastfeeding.
- The perception of risk measures were specific to long-term neurodevelopmental outcomes in offspring.
- The study included only women with a current/past mental illness, who are possible end users of antidepressants and other psychotropic drugs.
- Risk of bias due to self-selection cannot be excluded, although the results were made more generalizable in terms of age and county of residence by using survey weighting.
- A specific definition of all possible neurodevelopmental outcomes was not provided to respondents, and women rated their perceived drug risk on the broad, unspecific spectrum of child neurodevelopment.

Introduction

Maternal mental illness occurs in 5-15% of women during the perinatal period, most commonly major depression [1], anxiety [2,3], and eating disorders.[4] In addition to the difficulties associated with mental illness for the affected women themselves, these perinatal disorders pose risks for short- and long-term negative outcomes for offspring [5,6]. Women with a perinatal mental illness may therefore require psychotherapeutic or pharmacological treatment, or both, depending on the severity of the condition and therapeutic preference.

Antidepressants, particularly serotonin reuptake inhibitors (SSRIs), are the preferred pharmacological option for the above disorders during pregnancy [7]. Their estimated population prevalence, based on filled prescriptions during pregnancy, is 2.3-3.7% [8]. Other psychotropics, such as benzodiazepines, z-hypnotics and antipsychotics, are less often used [9,10]. Even though multiple studies have shown that antidepressants are not major teratogens [11–14], findings remain inconsistent about the risk of longer-term neurodevelopmental outcomes in children, e.g., attention-deficit/hyperactivity disorders (ADHD), autism spectrum disorder, or scholastic skills [15,16]. Current data about the reproductive safety of antipsychotics and benzodiazepines are limited [17–19], while the short- and long-term risk posed by the antiseizure drug valproate is now well-acknowledged [20,21].

In women with a perinatal mental illness, elevated risk perception of adverse outcomes in offspring due to psychotropic medication exposure often affects the decision-making regarding their treatment [22–24]. The ongoing debate concerning the reproductive safety of these medications may contribute to confusion and decisional conflicts regarding pharmacological treatment, both among women and healthcare providers [25,26]. Several studies have shown that the perceived teratogenic risk of psychotropic medication use may be unrealistically elevated among pregnant women or recent mothers [27,28]. In a multinational, web-based study across 18 countries, antidepressants were perceived as almost equally harmful for the

developing foetus as alcohol [28]. However, such risk was rated by the general population of pregnant women, irrespective of their mental illness and current or previous treatment with psychotropics. Understanding the perception of the risk of antidepressants and other psychotropics specifically in women with a mental illness is crucial, as they are possible end users of such medications. Given the uncertainties about the longer-term safety of antidepressants in pregnancy and the high decisional conflicts faced by women considering this treatment [15,29], quantifying the perceived medication risk specifically for long-term neurodevelopmental outcomes in children is clinically relevant.

In a sample of women with current or past mental illness, we aimed to examine the perception of risk of adverse long-term neurodevelopmental outcomes in offspring associated with prenatal and breastmilk exposure to antidepressant and other psychotropic medications, food items (alcohol and cranberries) and the mental illness itself. To contrast how women rated the perceived risk of antidepressant medication versus that of the mental illness itself, we sought to identify maternal factors associated with how these two risks were perceived.

Methods

Study design and participants

Participants were recruited from the HEALTHx2 study. HEALTHx2 is a cross-sectional, sequential mixed-methods study, in which data was collected from all regions of Norway between June 2020 and June 2021. The quantitative component preceded the qualitative one. The current study used solely quantitative cross-sectional data, which were collected using an electronic questionnaire administered via “Nettskjema” provided by the University of Oslo. Participants could choose to access the questionnaire anonymously or by using their national ID number. Information about the study was posted on multiple pregnancy and motherhood-related websites and apps, on social media, and brochures with the study information were

distributed at various psychiatric polyclinics, hospital psychiatric departments, and maternity health clinics (see eTable 1 for further detail). The complete questionnaire is presented in online Supplement 1. A pilot study was carried out in May 2020, which elicited no major changes to the questionnaire. Women were eligible to participate in the study if they: i) were between the ages of 18-55 years; ii) were planning a pregnancy, were pregnant or had given birth within the last 5 years (hereafter, recent mothers); and iii) have or had previously had a mental illness and been offered antidepressant treatment within the last 5 years.

Patient and public involvement

The research team attempted to involve patient representatives in the development of the study protocol and the questionnaire, with the support of national mental health patient organisations. No patient representatives were willing to be involved in this study.

Perception of risk

Participants were asked to rate (from 0 to 10, where 0 corresponded to 'not harmful' and 10 to 'very harmful') the perceived harmfulness of substances taken during gestation or while breastfeeding for the long-term neurodevelopment of the child in two separate questions, (i) in pregnancy and (ii) while breastfeeding. To enhance reliability, the question specified examples of long-term outcomes in offspring, specifically autism, motor development, language skills, and ADHD. The listed substances included antidepressants, antipsychotics, anxiety and sleeping medication, antiepileptics (e.g., valproate), mental illness *per se*, cranberries, and alcohol (e.g., wine, beer, spirit). The latter two exposures were listed to act as reference for not harmful and harmful exposures, respectively. Women were asked to check 'unknown substance' if they were unfamiliar with the substance. The risk perception measures were adapted from a prior study of perceived risk among pregnant women and new mothers [28].

Mental health factors

Previous and current mental health was measured via using self-report items in which participants could indicate the mental illness they currently or previously had within a predefined list including depression, anxiety, obsessive-compulsive disorders, eating disorders, other mental illness, and no mental illness. Participants were also asked to indicate the time points at which they had a mental illness according to their pregnancy status at the time of questionnaire completion. (i.e., planning a pregnancy, currently pregnant or recent mother; see eTable 2). To measure women's mental health burden, we counted the number of different illnesses reported across the available periods.

Active depressive symptoms were measured using the Edinburgh Postnatal Depression Scale (EPDS), a self-rating 10-item scale validated in pregnancy and postpartum for major and minor depression in clinical settings, with satisfactory Cronbach's alpha reliability (0.87) [30]. The EPDS has been previously validated in a Norwegian sample [31]. Women were asked to rate whether each item reflected how they had been feeling in the past seven days. Each item response scored 0-3 on an ordinal scale, producing a total EPDS score of 0-30. Higher scores indicate worse symptomatology. A cut-off score of 13 was used to determine the presence of active depressive symptoms; the choice of cut-off 13 is conservative, as it reflects the higher end of the validated cut-off for "probable depression" [30].

Current broadly-defined eating disorder subtypes (i.e., anorexia nervosa, bulimia nervosa, binge eating disorder (BED), eating disorder not otherwise specified purging type) were measured via items according to the DSM-IV criteria, by applying an algorithm used in a previous pregnancy cohort study in Norway [4] (see online Supplement 2).

Perceived stigma related to mental illness was measured using four selected items from the "Attitudes Toward Seeking Professional Psychological Help Scale" [32] (ATSPPHS).

Participants could indicate the extent to which they agreed or disagreed on each item, with a score ranging from 0 to 4. Scores across items were summed (range 0-20) and a greater score corresponded to more indifference to stigma (i.e., more positive attitudes). This was modelled as a numeric variable. The ATSPPHS was translated to Norwegian and back-translated using two independent translators.

Participants were also asked if they had previously received or were currently receiving psychological therapy (dichotomised as yes/no) and, if yes, the type of therapy and when they received it. Lastly, participants were asked to indicate the perceived effectiveness of antidepressants for treating mental illness both in general and during pregnancy, by rating this on a scale from 0 ('Not at all') to 10 ('Very useful'). See online Supplement 1 for further details.

Sociodemographic and life-style characteristics

These included women's age, county of residence, number of prior children, marital status, educational attainment and work situation at the time of conception (or current for pregnancy planners), body mass index (BMI) at time of conception (or current for pregnancy planners), having the Norwegian language as mother tongue, information about future pregnancies (if participants were planning to become pregnant shortly), the current pregnancy or the latest pregnancy. The questions were based on a prior web-based, cross-sectional study conducted among pregnant women in Norway [33]. To avoid data sparsity, maternal variables were categorized as shown in Table 1.

Statistical analysis

Mean risk perceptions and their 95% Confidence Intervals (CI) were assessed descriptively both for exposure in pregnancy and while breastfeeding, with survey weight adjustment (reported in the manuscript) and without survey weight adjustment (reported in eTable 3). The

survey weight was based on the most recent data available from the Norwegian Directorate of Health, which describes the proportion of female patients having had contact with psychiatric clinics in each health region of Norway (South-East, West, Middle, North) within each relevant age group (18-29, 30-39, 40-49 years) [34]. The weights were calculated by dividing the population proportion by the sample proportion in each age-by-region strata. This implies that the survey weight of underrepresented participants was larger than 1; that of overrepresented participants was smaller than 1. The mean survey weight of the sample was 0.7 (range = 0.3-13.3). Data on the county was missing for seven participants and the mean weight of the sample was assigned to these. There was no missing data for age. To appraise the impact of confounding by age and region on the perception of risk, we also conducted descriptive analyses with no survey weight.

Principal Component Analysis (PCA) was conducted to assess if the risk perception of the various substances could be grouped into fewer factors for analyses; due to the large proportion of women who indicated psychotropic drugs other than antidepressants as 'unknown', the PCA caused substantial data loss. As a result, the grouping of psychotropic drugs other than antidepressants was hindered, and we focused subsequent analyses on the perceived risk of antidepressant and maternal mental illness exposure only. A pre-registration [35] including the statistical analysis plan is published on the Open Science Framework (some sample statistics had been conducted before the publication of this pre-registration, but no analyses related to the outcomes).

Association analyses

To determine which factors were related to the rated risk of antidepressant and maternal mental illness during pregnancy and while breastfeeding, we conducted a series of multiple general linear models with a robust standard error, using the survey weight. These models were built following the 'purposeful selection' approach [36]. Candidate variables were first selected

based on a p-value < 0.15 in a univariable linear regression model. Selected candidate variables were then included in the multivariable model; at this stage, variables having no role (p-value > 0.05) or yielding a change smaller than 15% in the beta coefficients of the retained variables were removed. We examined a vast array of mental health and sociodemographic factors on risk perceptions. Candidate mental health variables included: current and active depressive symptoms, BED at the time of questionnaire completion, number of self-reported past or current mental illnesses, perceived stigma related to mental illness, psychological therapy, and perceived effectiveness of antidepressant treatment in general and during pregnancy. BED was the sole eating disorder included with a sufficient number of women to be included in the association analysis. Candidate demographic variables comprised marital status, work situation, education, having Norwegian as the main language, and woman's BMI. Missing data on mental health factors ranged from <1% to 33%, while this issue was minimal (<0.5%) for sociodemographic variables.

The final multiple regression model included statistically significant and clinically relevant factors (i.e., age, education). We replicated the multiple regression model in the three strata of women: planning a pregnancy at the time of questionnaire completion, being pregnant, or recent mothers. Among pregnancy planners, only demographic variables were included due to low sample size. Results are presented as mean difference in risk perception with the corresponding 95% CI, where positive coefficients indicated higher perceived risk and negative coefficients the converse.

Under the assumption that data were missing at random, we imputed incomplete data on the candidate explanatory variables and risk perception of antidepressants and maternal mental illness via multiple imputation with chained equation (twenty replications). The imputation model included the survey weight, baseline and health-related factors, and auxiliary variables. As sensitivity analysis, we ran mixed-effects models [37] to account for dependence within

different regions of Norway (North, South, East and West), and examined the distribution of key maternal variables by the number of "unknown" psychotropics reported. The intraclass correlation was below 0.05 in all models, indicating that similarity was low within regions. All statistical analyses were conducted using STATA MP v. 16.

Results

Of the 753 women who indicated their willingness to participate in the study, 500 (66% response rate) consented. After excluding participants with missing data for all risk perception substances, age < 18 years, and/or with no self-reported or proxies for current or previous mental illness, we reached a final study sample of 448 women. The data flow to achieve the final study sample is available in eFigure1. The background characteristics of the participants are summarised in Table 1. Most participants were either currently pregnant (52%) or recent mothers (33%). The mean gestational week of pregnant participants was 18.5 (SD = 9.8). The majority of recent mothers (61%) had a child between four and twelve months of age. Most planners (59%) were actively trying to conceive at the time of questionnaire response. The overall mean age was 30.8 years (*SD* = 4.6). The majority of women (75%) reported that they have or have had more than two psychiatric illnesses (see eTable 2), and 118 (26%) had active depressive symptoms. Broadly defined BED was observed in 85 (19%) women, and few (<15) were classified as having another eating disorder type.

Table 1: *Sociodemographic and health-related characteristics of the study sample (N =448)*

	N	%
Sociodemographic characteristics		
Age (years)		
18-29	170	38
30-49	278	62
Pregnancy status		
Planning a pregnancy	68	15
Currently pregnant	234	52
Recent mothers (within the last 5 years)	146	33
Geographical health region		
South-East Norway	261	59

	N	%
West Norway	98	22
Mid Norway	50	11
North Norway	32	7
Marital status		
Married or co-habiting	415	93
Single or divorced/separated	25	6
Other	8	2
Educational attainment (current or at time of conception)		
Primary school	21	5
High school	96	21
University/college	316	71
Other	14	3
Missing	<5	—
Work situation (current or at time of conception)		
Student	32	7
Homemaker	25	6
Health worker (e.g., medical doctor, nurse, pharmacist)	76	17
Other paid work	255	57
Job seeker	14	3
Other	46	10
Norwegian as main language		
Yes	405	91
No	42	9
Missing	<5	—
Health-related characteristics		
Self-reported number of mental illnesses[a]		
One	110	25
Two	172	38
Three or more	166	37
Current symptoms of depression/anxiety		
Yes (EPDS ≥ 13)	118	26
Missing	<5	—
Current broadly defined BED (yes)[b]	85	19
Had received or was currently receiving therapy		
Yes	230	51
No	208	46
Missing	10	2
	Mean	**SD**
Perceived stigma for mental illness[c,d]	9.1	4.1
Perceived effectiveness of antidepressant in general[c,e]	6.9	3.2
Perceived effectiveness of antidepressant in pregnancy[c]	5.3	3.9

Abbreviations: BED=Binge Eating Disorders; EPDS=Edinburgh Postnatal Depression Scale. There was no missing data for pregnancy status, marital status or work situation.
[a]Participants were asked about their history of mental illness; this figure comprise number of psychiatric illnesses from more than one year before to the time of questionnaire completion.
[b]Other EDs were also measured, but had low prevalence in the sample.
[c]Missing data were present for 4 (stigma scale), 7 (health region of residency), 85 (effectiveness of antidepressants in general), and 147 (effectiveness of antidepressants in pregnancy) women.
[d]Greater score corresponds to more indifference to stigma (i.e., more positive attitudes).
[e]Greater score corresponds to higher perceived effectiveness of antidepressants.

As shown in Table 2, cranberry and alcohol were perceived as the least and most harmful substances both in pregnancy and while breastfeeding, respectively. Among the psychotropic drugs, antidepressants were perceived as least harmful both in pregnancy (mean score 4.2, 95% CI: 3.6, 4.8) and breastfeeding (mean score 3.8, 95% CI: 3.3, 4.4). Participants rated the mental illness itself as somewhat more harmful than antidepressants in both exposure periods (mean scores of 5.9 and 5.6). The risk perception scores were lower in the survey-weighted analysis relative to the non-weighted (see eTable 3).

A large number of participants were unfamiliar with the risk of exposure to antipsychotics, anxiety and sleeping medication and antiepileptics. eTable 4 shows the descriptive statistics of risk perception excluding participants with missing or "unknown" responses to the risk perception items. The distribution of key characteristics according to rating as 'unknown" none, one, or more than one psychotropic is given in eTable 5.

Exposure to most substances was perceived as slightly less harmful in breastfeeding compared with during pregnancy, but the differences were small. The consistency of women's responses across the risk perception scores for psychotropics were 0.73 (pregnancy exposure) and 0.78 (breastfeeding exposure).

Table 2: *Descriptive statistics of the risk perception scores for seven items in relation to exposure during pregnancy and while breastfeeding*[a]

Substance	Mean risk score (SE)	95% CI	Median risk score	[Q1, Q3]	N	Unknown
Risk perception of exposures during pregnancy						
Alcohol	9.0 (0.1)	[8.7, 9.2]	10	[8, 10]	442	5
Antiepileptics	6.5 (0.4)	[5.6, 7.3]	7	[5, 9]	150	295
Antipsychotics	6.5 (0.3)	[5.9, 7.1]	7	[5, 9]	245	198
Anxiety and sleeping medication	6.3 (0.2)	[5.8, 6.7]	6	[5, 8]	328	116
Maternal mental illness *per se*	5.9 (0.2)	[5.4, 6.3]	6	[4, 8]	423	22
Antidepressants	4.2 (0.3)	[3.6, 4.8]	5	[3, 7]	383	63

Cranberry	0.9 (0.1)	[0.7, 1.1]	0	[0, 1]	301	143
Risk perception of exposures while breastfeeding						
Alcohol	7.0 (0.2)	[6.7, 7.4]	8	[5, 10]	437	9
Anxiety and sleeping medications	6.2 (0.3)	[5.6, 6.7]	6	[4, 9]	321	124
Antipsychotics	6.1 (0.3)	[5.5, 6.6]	6	[4, 9]	248	198
Maternal mental illness	5.6 (0.3)	[5.0, 6.2]	6	[3, 8]	417	26
Antiepileptics	5.5 (0.4)	[4.7, 6.3]	6	[4, 8]	152	293
Antidepressants	3.8 (0.3)	[3.3, 4.4]	4	[2, 6]	376	68
Cranberry	1.2 (0.2)	[0.7, 1.7]	0	[0, 1]	298	147

[a]These values were corrected by survey weight adjustment. Missing data was < 1.5% for all individual substances. Q1, Q3 indicates the interquartile range.

Figure 1 illustrates the perceived risk in pregnancy (Panel A) or while breastfeeding (Panel B) by pregnancy status (i.e., pregnancy planners, pregnant, or recent mothers). The risk perception was rated similarly by participants with different pregnancy statuses. However, antidepressant and mental illness exposures during pregnancy were perceived as slightly more harmful by pregnancy planners compared with pregnant participants.

Tables 3 and 4 report maternal factors associated with the perceived risks in pregnancy or while breastfeeding, respectively. Having primary school as the highest achieved education level, a non-Norwegian native language, and being a job seeker or homemaker, were the factors most strongly associated with greater antidepressant risk perception in both exposure periods among pregnancy planners (range of β: 2.07-6.07). Health workers rated the risk posed by maternal illness in both exposure periods significantly higher than women with other paid work (β: 1.72-2.35), but this association was solely present among pregnancy planners.

In both pregnant women and recent mothers, a greater perception of antidepressant effectiveness was associated with a lower risk rating of antidepressants in pregnancy or while breastfeeding, albeit the effect size was small (range of β: -0.18, -0.25). Mothers who were

unmarried/not cohabiting rated the risk of mental illness exposure in pregnancy significantly lower than the reference group (β: -6.30, 95% CI: -6.98, -5.61).

Table 3: *Factors associated with risk perception score for antidepressant and mental illness exposures during pregnancy, by pregnancy status*

	Antidepressants		**Maternal mental illness**	
Maternal predictive factor	*β [95% CI]*	*p-value*	*β [95% CI]*	*p-value*
Planning pregnancy				
Educational attainment				
High school	Ref		Ref	
Primary school	3.99 [2.62, 5.35]	<0.001	1.42 [0.16, 2.68]	0.027
University/college	1.59 [0.21, 2.98]	0.024	N.S.	—
Occupational status				
Other paid work	Ref		Ref	
Homemaker	1.89 [0.56, 3.22]	0.005	N.S.	—
Health worker	N.S.	—	1.72 [0.19, 3.26]	0.028
Job seeker / others	2.49 [0.90, 4.09]	0.002	N.S.	—
Not having Norwegian native language	3.30 [1.62, 4.98]	<0.001	N.S.	—
Pregnant				
AD effectiveness in pregnancy	-0.24 [-0.37, -0.10]	0.001	N.S.	—
Occupational status				
Other paid work	Ref		Ref	
Job seeker / others	-1.89 [-3.75, -0.02]	0.047	N.S.	—
Mothers				
Occupational status				
Other paid work	Ref		Ref	
Student	-1.73 [-3.14, -0.32]	0.016	N.S.	—
Homemaker	-2.19 [-3.90, .-0.47]	0.012	N.S.	—
Marital status				
Married or co-habiting	Ref		Ref	
Other	N.S.	—	-6.30 [-6.98, -5.61]	<0.001
Not having Norwegian native language	2.01 [0.53, 3.50]	0.008	N.S.	—
AD effectiveness in pregnancy	-0.18 [-0.37, -0.00]	0.049	N.S.	—

Notes. Only statistically significant factors are reported. All models were survey-weighted, and adjusted for age and education, in addition to the variables listed in the Table. Psychotherapy was retained in the model for pregnant women and antidepressant risk perception as its removal changed the beta coefficients of retained variable substantially.

Abbreviations: N.S.=non-significant statistically; AD=antidepressant.

Table 4: *Predictors of risk perception of antidepressant and mental illness exposures when breastfeeding, by pregnancy status*

	Antidepressants		**Maternal mental illness**	
Maternal predictive factor	*β [95% CI]*	*p-value*	*β [95% CI]*	*p-value*
Planning pregnancy				
Education				
High school	Ref		Ref	
Primary school	6.07 [4.38, 7.77]	<0.001	-2.34 [-4.08, -0.61]	0.008
University/college	1.66 [0.14, 3.17]	0.033	N.S.	—
Other	N.S.	—	4.75 [0.47, 9.03]	0.030
Occupational status				
Other paid work	Ref		Ref	
Homemaker	2.07 [0.69, 3.46]	0.003	-1.96 [-3.36, -.0.57]	0.006
Health worker	N.S.	—	2.35 [-0.04, 4.74]	0.054
Job seeker or other	2.53 [0.77, 4.30]	0.005	N.S.	—
Not having Norwegian native language	3.66 [1.75, 5.56]	<0.001	N.S.	—
Pregnant				
AD effectiveness in pregnancy	-0.24 [-0.39, -0.08]	0.003	N.S.	—
Stigma[a]	N. S.	—	-0.20 [-0.33, -0.07]	0.003
BED (Yes vs. No)	N. S.	—	1.66 [0.44, 2.88]	0.008
Mothers				
Occupational status				
Other paid work	Ref			
Student	-1.82 [-3.18, -0.47]	0.008	N.S.	—
Homemaker	-2.69 [-4.87, -0.51]	0.015		
Health worker	-1.31 [-2.61, -0.02]	0.047	N.S.	—
AD effectiveness in pregnancy	-0.25 [-0.45, -0.05]	0.014	N.S.	—

Notes. Only statistically significant factors are reported. All models were survey-weighted, and adjusted for age and education, in addition to the variables listed in the Table. Abbreviations: AD=antidepressant; BED=binge eating disorder; N.S.=non-significant statistically.

[a]Perceived stigma related to mental illness was measured using four selected items from the "Attitudes Toward Seeking Professional Psychological Help Scale

Discussion

This study is, to the best of our knowledge, the first to examine the perceived risk of adverse neurodevelopmental outcomes in offspring following exposure to psychotropic drugs and maternal mental illness itself during pregnancy or while breastfeeding. By targeting the evaluation of risk to women who are possible end users of psychotropics, the study generates

clinically relevant knowledge about barriers to the decision-making process regarding mental illness treatment in pregnancy or while breastfeeding.

We found that antidepressants were perceived as less harmful than other psychotropic drugs, alcohol, and the maternal mental illness itself, both in pregnancy and when breastfeeding. This is in contrast with a prior study [28] where antidepressants were rated almost as harmful as alcohol. The perceived risk among participants from Northern Europe in the study by Petersen et al. was also higher than in the current study. There are several possible reasons for these differences. Firstly, there is now greater availability of research data on the longer-term reproductive safety of antidepressants in 2020 compared with 2011, which may have reached the population to a larger degree [11–15]. Secondly, our study measured the perceived risk for neurodevelopmental outcomes in offspring, whereas prior work [28] focused on structural teratogenic risk. Thirdly, our participants had prior/current mental illness, increasing the likelihood that they would have received tailored counselling on potential risks of antidepressant exposure to the offspring. This could have contributed to a lower assessment of antidepressant risks. This finding is encouraging, as an overestimation of risk may contribute to treatment discontinuation and poor adherence, even when the antidepressant is needed [38].

A key result is that exposure to mental illness itself in pregnancy and when breastfeeding was perceived as more harmful than antidepressants, and almost at par with other psychotropics. In pregnant women, having BED was associated with a greater perceived risk of mental illness exposure in pregnancy and while breastfeeding, relative to women with no BED, which could be indicative of fears and concerns related to passing on the illness to the child and/or whether maternal eating patterns negatively affect the child [39]. Comparing this finding with prior research is difficult due to the lack of similar data. Nevertheless, it could point to greater awareness in women about the possible negative consequences of perinatal mental illness for offspring. This finding is important from both a public health and patient-specific perspective.

Confounding by maternal mental illness severity, genetic, and familial environment remains a concern when interpreting the associations between prenatal antidepressant exposure and child development [15]. Maternal perinatal mental illness has been linked to negative health outcomes in the mother [7], her offspring [5,40,41], and the family as a whole [42,43]. Negative sequelae include fewer mother-child interactions [44,45] and poorer long-lasting attachment bonds [46]. Therefore, in treating a perinatal mental illness, the potential risks of treatment with psychotropic medication must be balanced against the negative consequences of untreated maternal mental illness for each woman. Psychotherapy has moderate effectiveness on postpartum depression [47,48], and should always be offered as first-line and/or alongside psychotropic medication. Interventions which aim to strengthen social support have also been found to have moderate effects on postpartum depression [49].

Our observed heightened risk perceptions for antipsychotics and sleeping and anxiety medication in both pregnancy and while breastfeeding may be attributable, at least in part, to the scarcity of research on the longer-term reproductive safety of these medications [17–19]. For many women with psychotic episodes and bipolar disorders, antipsychotics constitute important treatment components [1,6,7]. Yet, scarcity of safety data poses serious challenges for clinicians, and women themselves [49]. Even though antidepressants are often taken together with other psychotropics [38,50], many women in our study were unfamiliar with antipsychotics and sleeping and anxiety drugs, and could not rate their risks. This unfamiliarity was more common in women not working as health care professionals and those with lower education.

In line with current recommendations and the available evidence [20,21], antiepileptics, in specific valproate, were correctly rated as moderately harmful in pregnancy. This greater awareness can be attributable to the nation-wide restrictions on valproate prescribing in fertile women, in force since 2018 [51,52]. Other antiepileptic drugs such as lamotrigine, have a more

favourable safety profile in pregnancy, and their benefits outweigh the risk posed by untreated epilepsy on maternal-child health [53]. Because our questionnaire listed only valproate as an example for antiepileptics, the observed perceived risk most certainly relates to valproate only, and not to other antiepileptic drugs.

Generally, women did not seem to differentiate between risks of exposure in pregnancy and when breastfeeding to a substantial degree, which is surprising. Clinicians should be aware of this perception, so that they can adequately inform women about the difference in risk during pregnancy or while breastfeeding. Although data on psychotropic excretion into breastmilk and possible effects on the breastfed infant are sparse, most psychotropics are considered compatible with breastfeeding [53]. Breastfeeding is strongly recommended to improve maternal and child health outcomes [54], and in most cases the benefit of breastfeeding outweighs the potential risks to the infant. However, for specific drugs, e.g., lamotrigine or second-generation antipsychotics, an individual assessment needs to be performed, which includes consideration of infant age, maternal wish to breastfeed, and safer treatment alternatives [53].

Among pregnancy planners, sociodemographic characteristics such as having primary school as the highest education level, non-Norwegian native language, and being unemployed or a homemaker, were associated with increased perceived risk of antidepressant exposure in pregnancy and breastfeeding. Differential access to healthcare and evidence-based counselling, as well as the ability to obtain and interpret health information, could in part contribute to these results. These groups of women should be primary targets for preconception intensified counselling. The association between greater perception of antidepressant effectiveness and lower risk rating of these drugs in pregnancy may point to an increased emphasis on the woman's needs regarding treatment in the perinatal period. Even though the available evidence on antidepressant effectiveness in pregnancy is limited [55], the psychiatric history of the

woman, her response to prior and/or ongoing antidepressant treatment, and outcomes following prior attempts to discontinue the medication, must be part of the individual risk-benefit assessment of antidepressants in pregnancy and while breastfeeding. Such assessment should always be done together with the woman as part of the shared decision-making.

Strengths and limitations

One major strength of our study is that risk perceptions were measured using the same methodology as in prior research [28], with the added advantage of being specific to perceived risk of neurodevelopmental outcomes in offspring. The study had a considerable study size given the difficult-to-reach population, from all regions of Norway. Several recruitment strategies were implemented to minimize the risk of selection bias. To make the sample more representative, analyses were corrected using survey weight adjustment based on the most recent data from the Norwegian Health Directorate; however this affected our results only minimally [34]. The study used screening tools and diagnostic algorithms validated and/or used in prior research in Norway [4,31]. We also conducted multiple imputation for missing data on both explanatory and outcome variables. The primary analyses of the current study were pre-registered [35], although some sample descriptive statistics had been conducted before the pre-registration.

Our study also has limitations. The sample size for women planning a pregnancy was low, and a large proportion of participants were unfamiliar with antipsychotics, antiepileptics and anxiety and sleeping medication. It is possible that naming branded products could have enhanced recall. Unfamiliarity with these psychotropics was more common among women not working as a healthcare professional and those with lower education. This could have influenced our descriptive and association results, although the latter were all adjusted for maternal educational level. An important limitation of the study is that we did not provide a specific definition of all individual 'neurodevelopmental outcomes' in the questionnaire, but

rather presented a few substantially heterogeneous examples. This may have affected the accuracy of women's reporting on the perceived risk of psychotropics and mental illness on the broader, unspecific domain of child neurodevelopment. We cannot rule out the possibility that the lack of clarity in these items influenced our estimates of perceived risk and associations. The mental illnesses were self-reported by the participants, and thus dependent on the accuracy of the woman's reporting. However, the eligibility criteria included being offered antidepressant treatment in the last 5 years, thus targeting primarily moderate to severe mental illness cases. Women with no proxy of current/past mental illness were excluded from the analysis. Use of an electronic questionnaire and multiple recruitment strategies did not permit calculation of a conventional response rate, and bias due to self-selection cannot be ruled out. However, among the women expressing their willingness to participate or not in the study, the response rate was satisfactory (66%). The validity of web-based recruitment methods is now well-acknowledged [56,57], and the internet penetration rate is almost 100% in women of childbearing age in Norway [58]. We did not consider how patterns of psychotropic medication use were related to the woman's assessment of their risk. We assumed data to be missing at random when conducting the association models; however this assumption is not testable and it was only based on the patterns of missingness in our population. Finally, we cannot exclude the possibility that the women who decided to participate in the study differed from the general birthing population of women with mental illnesses in ways that our analysis could not control for.

Conclusion

In this population, the perceived risk of maternal mental illness exposure during pregnancy or while breastfeeding on child neurodevelopment exceeded that for antidepressants. Exposure to antiepileptics, antipsychotics, anxiety and sleeping medication was perceived as most harmful, together with alcohol. Specific sociodemographic variables and perceived effectiveness of

antidepressants were significantly associated with rated risk of antidepressants and mental illness. Our findings underline the importance of providing tailored, evidence-based information about the benefits and risks of both psychotropic and mental illness exposure during pregnancy or while breastfeeding, to facilitate complex shared decision-making.

CONTRIBUTORSHIP: AL conceived the idea for the study; AL, LDB and FT participated in its design and coordination. LDB and AL drafted the manuscript and analyzed the data. AL, LDB, FT, KSH, HKC, KH contributed to the data collection. All authors contributed to the interpretation of the results and revised the manuscript critically for important intellectual content. All the authors read and approved the final manuscript.

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DATA SHARING: All data relevant to the study are included in the article or uploaded as supplementary information. Researchers can apply for data access for subprojects within the overall aims of the main study 'HEALTHx2'.

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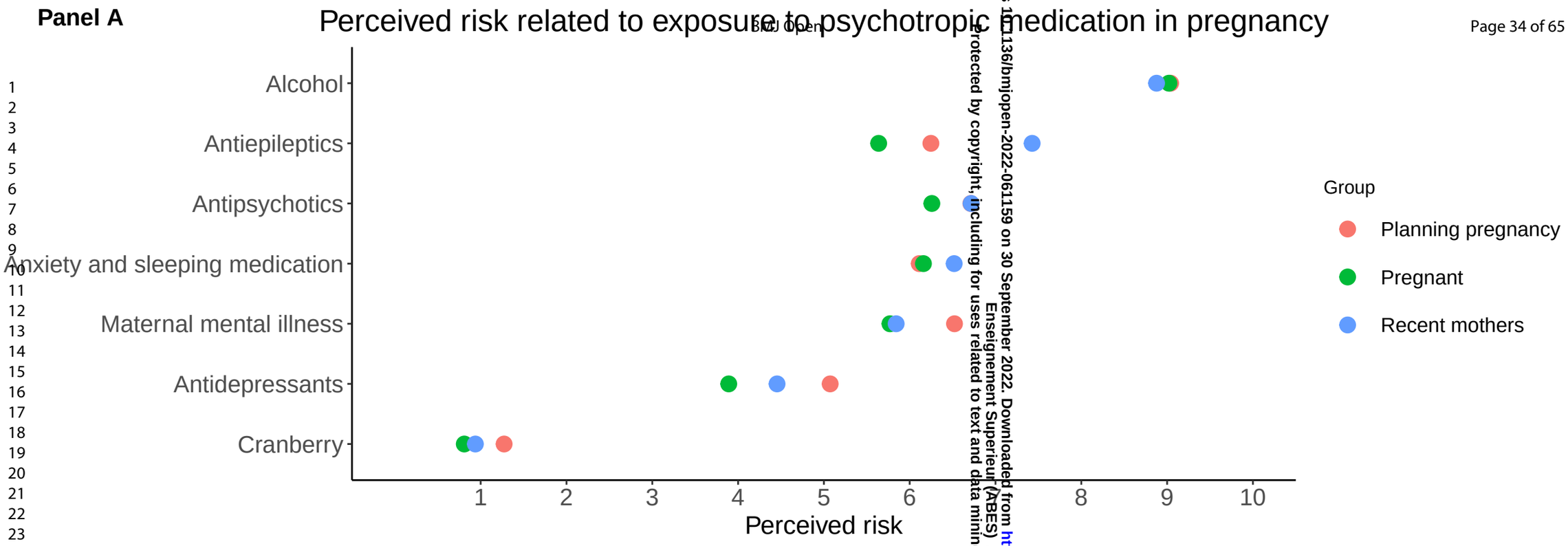
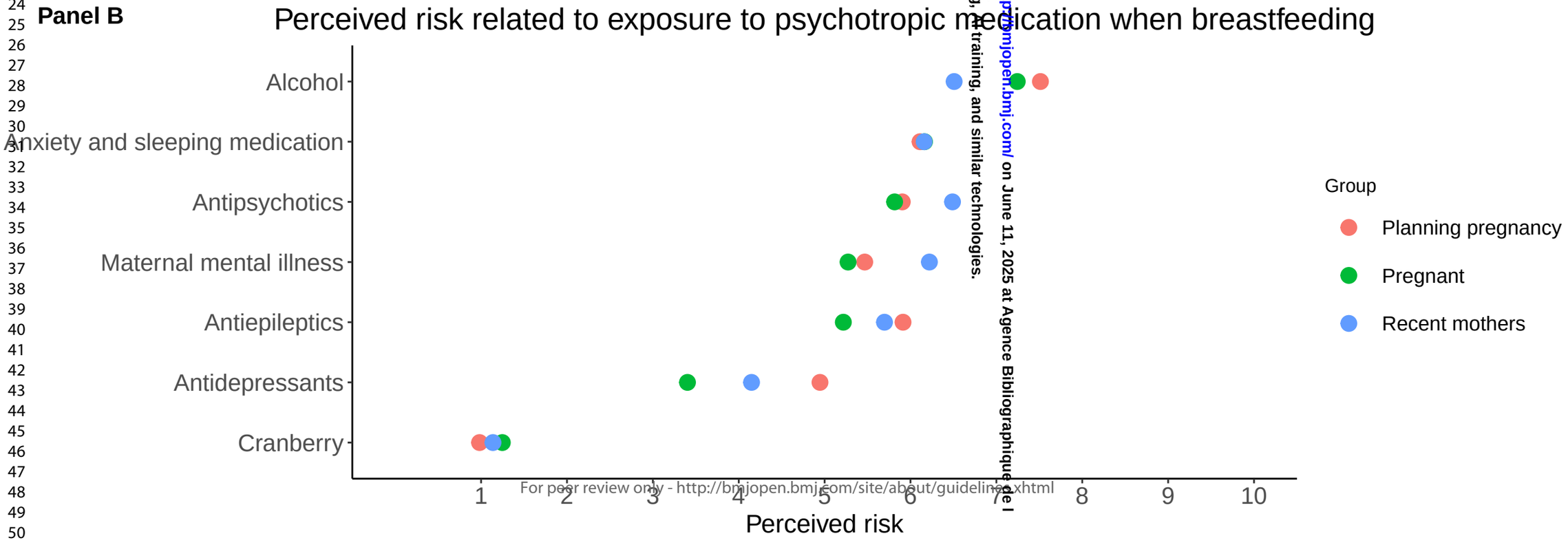
Figure legend

Figure 1: *Perceived Weighted Risk Related to Exposure in Pregnancy (Panel A) and while breastfeeding (Panel B)*

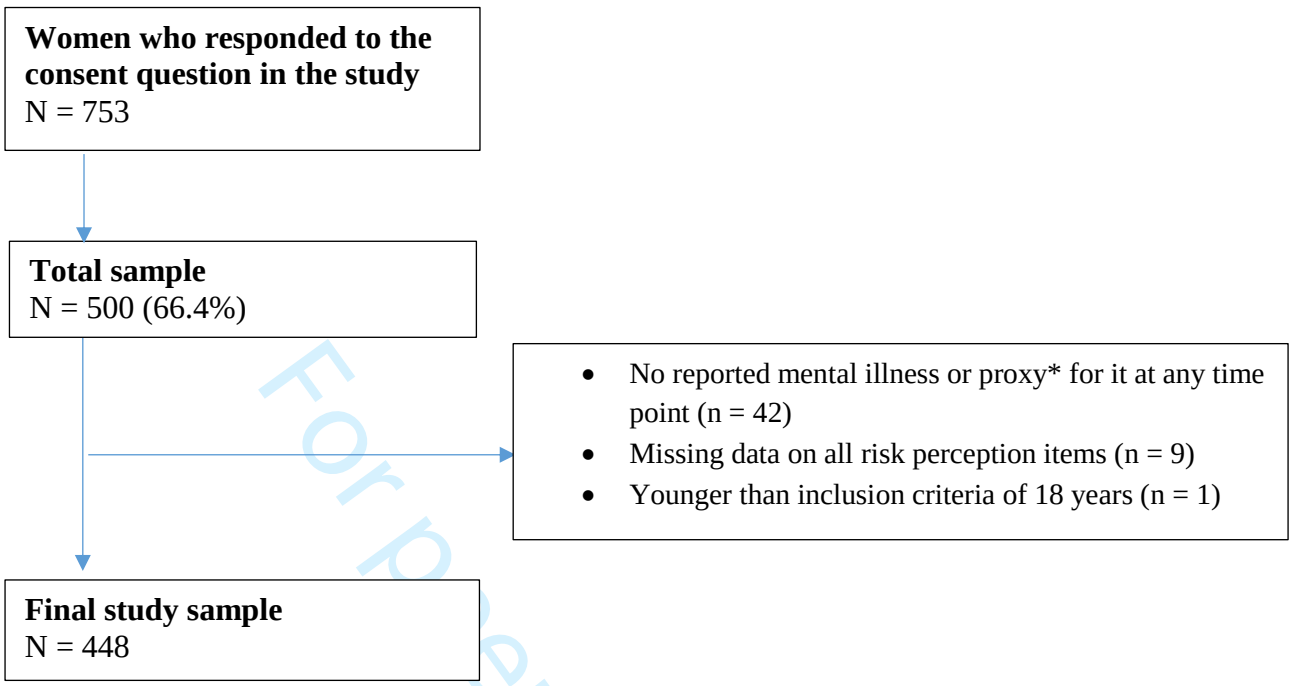
Panel A



Panel B



e-Only Figure 1: Data flow to achieve the final study sample



*Proxies of mental illness included having used a psychotropic medication or non-pharmacological psychotherapy in the past or currently, having an eating disorder according to the DSM-IV algorithm, having active depressive symptoms or self-harm thoughts at the time of questionnaire response as measured by the EPDS scale, or the PHQ2 scale. These proxies were used to verify whether women with missing or no reported mental illness based on self-reported diagnoses, had proxies of mental illness (since this was an eligibility criterion in the study).

e-Table 1: Recruitment strategies used in the study, including psychiatric clinics, websites, apps and social media

Recruitment strategy 1: Informative brochures about the study available at the site, which could be taken freely by the participants	
Site specification/type	*Site location(s)*
Psychiatric outpatient polyclinics	Østre Agder, Lister, Flekkefjord, Solvang, Strømme (Agder region); Lørenskog (Viken region); North of Norway (Tromsø and surrounding areas)
Outpatient polyclinic for anxiety	Flekkefjord (Agder region))
Specialized outpatient polyclinic of psychosomatics and trauma	Lundsiden (Agder region))
Psychiatric hospital ward	Hospital of South Norway (Sørlandet sykehus), Akershus Universitetssykehus HF in Lørenskog (Viken region)
Regional Section for Eating Disorders	Oslo University Hospital, Villa Sult in Oslo
Public prenatal and postnatal care health clinics	Oslo (Grunerløkka district, Østensjø), Stavanger, Bergen, Trondheim, Tromsø, Ås, Tingvoll, Hareid
Recruitment strategy 2: Information about the study on selected pregnancy-motherhood specific websites, as well as medically oriented websites in Norwegian language, social media and pregnancy forums	
General pregnancy / motherhood specific websites or Facebook page	www.ammehjelp.no (breastfeeding support network), www.altformamma.no (general website for mothers),
Medical-specific websites	www.hjelptilhjelp.no (portal for mental health); www.nhi.no (health portal for healthcare personnel and lay persons); www.tryggmammamedisin.no (National medicines information centre for pregnant and breastfeeding women)
Social media	Facebook (featured ads and posts in pregnancy-related and mental health-related pages and groups), Twitter, featured google ads
Pregnancy forums	Kvinneguide (forum for women in general)
Recruitment strategy 3: Information about the study distributed by patient organizations and peers via social media	
Social media	Organization «Psykisk helse» (Mental health) via Twitter; organization "Landsforening1001dager» (perinatal mental health organization) via their Facebook page; "Norske Kvinners Sanitetsforening" (Women association of Norway) via their Facebook and twitter page

Recruitment strategy 4: Information about the study distributed to users of pregnancy-specific or women-specific apps	
Apps	"Clue", an app to track ovulation and pregnancy planning; "Helseoversikt", an app recommended by all prenatal and postnatal health centres in Norway to track health appointments for mother and child, and other health-related information on pregnancy, motherhood and infant care

e-Table 2: Type of reported mental illnesses in women planning a pregnancy (2a), mothers or pregnant (2b)

2.a*: Self-reported Mental Illness Among Women Planning to Become Pregnant (N = 68)*[*]

Self-reported illness	More than one year ago	Within the last year	Currently
Depression	24	20	24
Anxiety	15	18	28
OCD	10	2	2
ED	19	4	5
Other mental illness	9	6	11

*Women could report more than one time point for each mental illness.

Abbreviations: OCD=Obsessive-compulsive disorders; ED=Eating Disorders.

2.b: *Self-reported Mental Illness Among Pregnant Women or Recent Mothers (N = 380)*[*]

Self-reported illness	Before pregnancy	During 1st trimester	During 2nd trimester	During 3rd trimester	After birth
Depression	346	84	51	48	101
Anxiety	323	88	64	60	102
OCD	51	10	6	5	17
ED	105	17	9	12	22
Other mental illness	79	20	12	11	26

*Women could report more than one time point for each mental illness.

Abbreviations: OCD=Obsessive-compulsive disorders; ED=Eating Disorders.

e-Table 3: Non-weighted mean risk perception of exposures during pregnancy and while breastfeeding

Substance	Mean risk score (SE)	95% CI	Median risk score	[Q1, Q3]	N
Risk perception of exposures during pregnancy					
Alcohol	9.0 (0.1)	[8.8, 9.2]	10	[8, 10]	442
Antipsychotics	6.8 (0.2)	[6.5, 7.2]	7	[5, 9]	245
Antiepileptics	6.6 (0.2)	[6.1, 7.0]	7	[5, 9]	150
Anxiety and sleeping medications	6.4 (0.1)	[6.1, 6.7]	6	[5, 8]	328
Maternal mental illness *per se*	5.8 (0.1)	[5.5, 6.0]	6	[4, 8]	423
Antidepressants	4.7 (0.1)	[4.4, 4.9]	5	[3, 7]	383
Cranberry	1.0 (0.1)	[0.8, 1.2]	0	[0, 1]	301
Risk perception of exposures while breastfeeding					
Alcohol	7.1 (0.1)	[6.8, 7.4]	8	[5, 10]	437
Antipsychotics	6.3 (0.2)	[5.9, 6.6]	6	[4, 9]	248
Anxiety and sleeping medications	6.1 (0.2)	[5.8, 6.4]	6	[4, 9]	321
Antiepileptics	6.0 (0.2)	[5.5, 6.4]	6	[4, 8]	152
Maternal mental illness *per se*	5.6 (0.2)	[5.3, 5.9]	6	[3, 8]	417
Antidepressants	4.3 (0.1)	[4.0, 4.6]	4	[2, 6]	376
Cranberry	1.0 (0.1)	[0.7, 1.2]	0	[0, 1]	298

e-Table 4: Descriptive statistics of risk perception for participants who had no missing responses and no 'unknown' responses for the risk perception items (N = 125), weighted

Substance	Mean risk score (SE)	95% CI
Risk perception of exposures during pregnancy		
Alcohol	8.5 (.3)	[8.0, 9.0]
Antiepileptics	6.7 (.3)	[6.2, 7.3]
Antipsychotics	6.7 (.3)	[6.1, 7.3]
Anxiety and sleeping medications	6.6 (.2)	[6.2, 7.1]
Maternal mental illness *per se*	5.9 (.3)	[5.2, 6.5]
Antidepressants	4.6 (.3)	[4.0, 5.3]
Cranberry	1.1 (.2)	[.7, 1.5]
Risk perception of exposures while breastfeeding		
Alcohol	6.4 (.4)	[5.7, 7.1]
Anxiety and sleeping medications	6.3 (.2)	[5.8, 6.8]
Antiepileptics	6.1 (.3)	[5.6, 6.6]
Antipsychotics	6.1 (.3)	[5.5, 6.8]
Maternal mental illness *per se*	6.1 (.3)	[5.5, 6.6]
Antidepressants	4.2 (.3)	[3.5, 4.9]
Cranberry	1.2 (.3)	[.6, 1.8]

e-Table 5: Distribution of key maternal characteristics by number of psychotropic medication risk rated as "unknown" by women for exposure in pregnancy and while breastfeeding

	Number of "unknown" responses in relation to risk perception of all listed psychotropic medications during pregnancy			Number of "unknown" responses in relation to risk perception of all listed psychotropic medications while breastfeeding		
	None (n=144)	One psychotropic (n=105)	More than one psychotropic (n=199)	None (n=150)	One psychotropic (n=150)	More than one psychotropic (n=198)
	n (%)	*n (%)*	*n (%)*	*n (%)*	*n (%)*	*n (%)*
Age (years)						
18-29	48 (33.3)	45 (42.9)	77 (38.7)	53 (35.3)	42 (42.0)	75 (37.9)
30-49	96 (66.7)	60 (57.1)	122 (61.3)	97 (64.7)	58 (58.0)	123 (62.1)
Educational attainment (current or at time of conception)						
Primary school	6 (4.2)	<5	12 (6.0)	6 (4.0)	<5	12 (6.1)
High school	26 (18.1)	28 (26.7)	42 (21.1)	28 (18.7)	26 (26.0)	42 (21.2)
University/college	110 (76.4)	72 (68.6)	134 (67.3)	114 (76.0)	70 (70.0)	132 (66.7)
Other	<5	<5	10 (5.0)	<5	<5	11 (5.6)
Missing	-	-	-	-	-	<5
Work situation (current or at time of conception)						
Student	13 (9.0)	6 (5.7)	13 (6.5)	13 (8.7)	5 (5.0)	14 (7.1)
Homemaker	8 (5.6)	8 (7.6)	9 (4.5)	8 (5.3)	9 (9.0)	8 (4.0)
Health worker	48 (33.3)	9 (8.6)	19 (9.6)	49 (32.7)	8 (8.0)	19 (9.6)
Other paid work	54 (37.5)	66 (62.9)	135 (67.8)	59 (39.3)	63 (63.0)	133 (67.2)
Job seeker / Other	21 (14.6)	16 (15.2)	23 (11.6)	21 (14.0)	15 (15.0)	24 (12.1)
Norwegian as main language						
Yes	131 (91.0)	90 (85.7)	184 (92.5)	135 (90.0)	86 (86.0)	184 (92.9)
No	13 (9.0)	14 (13.3)	15 (7.5)	14 (9.3)	14 (14.0)	14 (7.1)
Missing	-	<5	-	<5	-	-
Self-reported number of mental illnesses						
One	33 (22.9)	22 (21.0)	55 (27.6)	35 (23.3)	21 (21.0)	54 (27.3)
Two	50 (34.7)	42 (40.0)	80 (40.2)	49 (32.7)	41 (41.0)	82 (41.1)
Three or more	61 (42.4)	41 (39.1)	64 (32.2)	66 (44.0)	38 (38.0)	62 (31.3)

HEALTHX2 - PATIENT-CENTERED APPROACHES TO AID WOMEN'S DECISION-MAKING AND SET PRIORITIES IN PERINATAL ANTIDEPRESSANT RESEARCH

electronic questionnaire

INFORMATION ABOUT YOURSELF

1. **In which region/province do you live?**
   Region:

2. **Please specify your current pregnancy status**.
   ☐ I am pregnant
   ☐ I have recently given birth (in the last year)
   ☐ I have given birth in the last 5 years

3. (If yes "I am pregnant): **In which pregnancy week are you?**
   From 1 to 44

4. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **How old is your child?**
   ☐ less than 1 month
   ☐ 1-3 months
   ☐ 4-6 months
   ☐ 7-9 months
   ☐ 10-12 months
   ☐ 1-5 years

5. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **Are you currently breastfeeding or have you breastfed your child?**
   ☐ Yes ☐ No

6. (If yes "Are you currently breastfeeding or have you breastfed your child?): **What kind of breastfeeding?**
   ☐ Exclusive with breastmilk from 0 to 4-6 months ☐ Partial with formula/milk from 0 to 4-6 months

7. **Have you been pregnant before? (This also applies to pregnancy that ended in abortion, miscarriage or fetal death)**
   ☐ Yes ☐ No

8. **How many children do you have now?**
   ☐ None ☐ 1 ☐ 2 ☐ more than 2

9. **What is your marital status?**
   ☐ Married ☐ Cohabitant ☐ Single ☐ Divorced/Separated
   ☐ Other/Please specify:_____

10. **What is the highest education you have completed?**
    ☐ Primary school (10 years of education)
    ☐ High-school (11-13 years of education)
    ☐ University / college
    ☐ Other/Please specify: _____

11. **Your age (in years)?**
From 15 to 55:

12. **Is Norwegian your mother tongue?** ☐ Yes ☐ No

13. **How tall are you (in cm)**?_____

14. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"): **What was your weight at the time of conception (in kg)?** _____

15. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years" or "I am planning a pregnancy"): **What is your current weight now (in kg)?** _____

INFORMATION ABOUT YOUR FUTURE PREGNANCY

(If yes to "I am planning a pregnancy"), for questions 16-19:

16. **When are you planning to get pregnant?**

☐ Within the next 6 months ☐ Within one year ☐ More than 1 year from now

17. **Are you currently trying to conceive?**

☐ Yes ☐ No ☐ Other, please specify_____

18. **Do you smoke cigarettes?**

☐ No ☐ Sometimes ☐ Daily

19. **What is your current work situation?**

☐ Student
☐ Homemaker
☐ Health care personnel, i.e., physician, nurse, or pharmacist
☐ Employed in another sector
☐ Job seeker
☐ None of the above, specify:_____

INFORMATION ABOUT YOUR CURRENT OR LATEST PREGNANCY

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years") for questions 20-23:

20. **Was your pregnancy planned?**

☐ Yes ☐ No, but it was not completely unexpected ☐ No, it was not planned

21. **Did you drink any alcohol after finding out that you were pregnant?**

☐ Yes ☐ No ☐ cannot remember

22. **Did you smoke after finding out you were pregnant?**

☐ No ☐ Sometimes ☐ Daily

23. **What was your work situation when you became pregnant?**

☐ Student
☐ Homemaker
☐ Health care personnel, i.e., physician, nurse, or pharmacist
☐ Employed in another sector
☐ Job seeker
☐ None of the above, specify:_____

HOW YOU ARE DOING AND YOUR MEDICATION USE

The next questions are about your well-being and your use of medication.

24. (If yes to "I am planning a pregnancy"). **Do you have you or have you had any of the following mental illnesses or health problems? If yes, check the box when you have experienced the illnesses.**

	More than 1 year ago	Within the last year	Currently
☐ Depression	☐	☐	☐
☐ Anxiety	☐	☐	☐
☐ Obsessive Compulsive disorder	☐	☐	☐
☐ Eating disorder (for example bulimia, anorexia, binge eating)	☐	☐	☐
☐ Other mental illness	☐	☐	☐
☐ No mental illness	☐	☐	☐

25. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **Have you or have you had any of the following mental illnesses or health problems in the period around your pregnancy? If yes, check the box when you have experienced the illnesses. Please choose the alternatives that apply to you**.

	More than 1 year before pregnancy	1 year or less before pregnancy	In 1st trimester	In 2nd trimester	In 3rd trimester	0 to 6 months after birth	7 to 12 months after birth
☐ Depression	☐	☐	☐	☐	☐	☐	☐
☐ Anxiety	☐	☐	☐	☐	☐	☐	☐
☐ Obsessive Compulsive disorder	☐	☐	☐	☐	☐	☐	☐
☐ Eating disorder (for example bulimia, anorexia, binge eating)	☐	☐	☐	☐	☐	☐	☐

☐ Other mental illness	☐	☐	☐	☐	☐	☐	☐
☐ No mental illness	☐	☐	☐	☐	☐	☐	☐

26. (If yes to "I am planning a pregnancy"). **If you have recently received or receive now psychological treatment (e.g. therapy) for your mental illness, please specify which and when**:

☐ Yes, I receive or have recently received psychological treatment

☐ No, I do not receive or have not recently received any psychological treatment

27. (If yes in question 26). **If yes, what kind? (for example individual psychotherapy, group therapy, counselling session)**_____

28. (If yes in question 26): **If yes, when?**

More than 1 year ago	Within the last year	Currently
☐	☐	☐

29. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **If you have recently received or receive now psychological treatment (e.g. therapy) for your mental illness, please specify which and when**:

☐ Yes, I receive or have recently received psychological treatment

☐ No, I do not receive or have not recently received any psychological treatment

30. (If "Yes in question 29) **If yes, what kind? (for example individual psychotherapy, group therapy, counselling session)**_____

31. (If "Yes in question 29) **If yes, when?**

More than 1 year before pregnancy	1 year or less before pregnancy	In 1st trimester	In 2nd trimester	In 3rd trimester	0 to 6 months after birth	7 to 12 months after birth
☐	☐	☐	☐	☐		

32. **During the past month: have you often been bothered by feelings of sadness, depression or hopelessness?**

☐ Yes ☐ No

33. **During the past month: have you often been bothered by having less interest in things or less pleasure in doing things?**

☐ Yes ☐ No

The next 10 questions are about how you have been doing it for the last 7 days. There are no right or wrong answers. We are only interested in your personal views. (Tick only one box per question)

In this section of the questionnaire - questions 34-43 - ***the Edinburgh Postnatal Depression Scale (EPDS)*** *was presented (Cox J, Holden J, Sagovsky R. Detection of postnatal depression. Development of the 10-item edinburgh postnatal depression scale. The British Journal of Psychiatry. 1987 June 1, 1987;150(6):782-6).*

The next questions are about your weight and weight control.

(If yes to "I am planning a pregnancy"), for questions 44-45

44. **Do you think you are overweight now that you plan a pregnancy?**

- ☐ Yes, a lot
- ☐ Yes, little
- ☐ No

45. **Are you or have you been worried about putting on more weight than necessary during a pregnancy?**

- ☐ Yes, very worried
- ☐ Somewhat worried
- ☐ No, not especially worried

46. (If yes "I am pregnant): **Do you think you were overweight just before this pregnancy?**

- ☐ Yes, a lot
- ☐ Yes, little
- ☐ No

47. (If yes "I am pregnant): **Are you or have you been worried about putting on more weight than necessary during this pregnancy?**

- ☐ Yes, very worried
- ☐ Somewhat worried
- ☐ No, not especially worried

48. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **Do you think you were overweight just in this period:**

	Yes, a lot	Yes, a little	No
Just before the pregnancy	☐	☐	☐
During pregnancy	☐	☐	☐
The first 12 months after birth	☐	☐	☐

49. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **Are you or have you been worried about putting on more weight than necessary in this period:**

	Yes, very worried	Somewhat worried	No, not especially worried
During the last pregnancy	☐	☐	☐
The first 12 months after my latest birth	☐	☐	☐

50. **Has anyone said that you were too thin while you felt that you were overweight during the last 2 years?**
    - ☐ Yes, often
    - ☐ Yes, occasionally
    - ☐ No

(If yes to "I am planning a pregnancy"), for questions 51-52

51. **Have you ever felt that you lost control while eating and were not able to stop before you have eaten far too much?**

	Last 6 months	Currently
No	☐	☐
Infrequently	☐	☐
Yes, at least once a week	☐	☐

52. **Have you used any of the following methods to control your weight during the last 6 months?**

Vomiting	☐ **Atleast once a week**	☐ **Seldom**	☐ **Never**
Laxatives	☐ Atleast once a week	☐ Seldom	☐ Never
Fasting	☐ Atleast once a week	☐ Seldom	☐ Never
Hard physical exercise	☐ Atleast once a week	☐ Seldom	☐ Never

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"), for questions 53-55

53. **Have you ever felt that you lost control while eating and were not able to stop before you have eaten far too much? (remember to choose only the period relevant for you)**

	Last 6 months before this pregnancy	During pregnancy	The first 12 months after birth
No	☐	☐	☐
Infrequently	☐	☐	☐
Yes, at least once a week	☐	☐	☐

54. **Have you used any of the following methods to control your weight during the last 6 months before pregnancy?**

Vomiting	☐ Atleast once a week	☐ Seldom	☐ Never
Laxatives	☐ Atleast once a week	☐ Seldom	☐ Never
Fasting	☐ Atleast once a week	☐ Seldom	☐ Never
Hard physical exercise	☐ Atleast once a week	☐ Seldom	☐ Never

55. **Have you used any of the following methods to control your weight during pregnancy?**

Vomiting	☐ Atleast once a week	☐ Seldom	☐ Never
Laxatives	☐ Atleast once a week	☐ Seldom	☐ Never
Fasting	☐ Atleast once a week	☐ Seldom	☐ Never
Hard physical exercise	☐ Atleast once a week	☐ Seldom	☐ Never

(If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"):

56. **Have you used any of the following methods to control your weight during the first 12 months after pregnancy?**

Vomiting	☐ Atleast once a week	☐ Seldom	☐ Never
Laxatives	☐ Atleast once a week	☐ Seldom	☐ Never
Fasting	☐ Atleast once a week	☐ Seldom	☐ Never
Hard physical exercise	☐ Atleast once a week	☐ Seldom	☐ Never

57. **Is it important for your self-image that you maintain a certain weight?**

☐ Yes, very important
☐ Yes, quite important
☐ No, not especially important

The next questions are about your views about use of antidepressant medication during pregnancy.

58. **Have you previously taken or are you currently taking antidepressant medications?**

☐ Yes, I have previously taken and/or I am currently taking antidepressant medication
☐ No

59. **What is your preference regarding treatment with antidepressant during pregnancy?**

☐ Continue treatment with the same antidepressant(s)
☐ Switch to another antidepressant
☐ Discontinue use of the antidepressant
☐ Reduce the dose of the antidepressant
☐ No preference
☐ Other, specify:_____

60. **Do you think that antidepressants can be safely used in all phases of pregnancy? (You can choose multiple answers)**

☐ No
☐ A woman should receive tailored counselling to facilitate her decision-making whether to take medications or not
☐ Use has to be stopped because it is harmful to the unborn child
☐ Use must not be discontinued, because this can be harmful for maternal mental health
☐ No preference
☐ Other, specify:_____

61. (If yes to "I am planning a pregnancy"). **The next questions are about your treatment with antidepressant medication. If you are taking now or have taken antidepressant medication for your mental illness in the last 6 months, please select the relevant antidepressants from the list below and when you used them. If you did not take antidepressant, you can skip this question**.

	Last 6 months	Now
☐ Fluoxetine (incl. Fontex, etc)	☐	☐
☐ Fluoxetine (incl. Fluoxetin Mylan, Fluoxetine Orion, Fontex)	☐	☐
☐ Citalopram (incl. Cipramil Farmagon, Cipramil Lundbeck, Citalopram Sandoz)	☐	☐
☐ Escitalopram (incl. Cipralex Farmagon, Cipralex Lundbeck, Escitalopram Actavis)	☐	☐
☐ Paroxetine (incl. Seroxat, Paroxetin Actavis, Paroxetin Farmagon)	☐	☐
☐ Sertraline (incl. Sertralin HEXAL, Zoloft, Sertraline Accord)	☐	☐
☐ Fluvoxamine (incl. Fevarin Mylan, Fevarin Orifarm)	☐	☐
☐ Venlafaxine (incl. Efexor, Venorion, Venlazid, Venlafaxin Bluefish)	☐	☐
☐ Duloxetine (incl. Cymbalta, Duloxetin Pensa, Duloxetine Mylan)	☐	☐
☐ Mirtazapine (incl. Remeron, Mirtazapin Bluefish)	☐	☐
☐ Reboxetine (incl. Edronax)	☐	☐
☐ Mianserin (incl. Mianserin Mylan, Tolvon)	☐	☐
☐ Amitriptyline (incl. Anafranil, Klomipramin Mylan)	☐	☐
☐ Clomipramine (incl. Anafranil, Klomipramin Mylan)	☐	☐
☐ Trimipramine (incl. Surmontil)	☐	☐
☐ Nortriptyline (incl. Noritren)	☐	☐
☐ Doxepine (inkl. Sinequan)		

62. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **The next questions are about your treatment with antidepressant medication. If you are taking now or have taken antidepressant medication for your mental illness in the period around pregnancy, please select the relevant antidepressants from the list below and when you used them. (Remember to choose relevant alternatives). If you did not take antidepressant, you can skip this question**.

	More than 6 months before pregnancy	6 months or less before pregnancy	1st trimester	2nd trimester	3rd trimester	0 to 6 months after birth	7 to 12 months after birth
☐ Fluoxetine (incl. Fluoxetin Mylan, Fluoxetine Orion, Fontex)	☐	☐	☐	☐	☐	☐	☐
☐ Citalopram (incl. Cipramil Farmagon, Cipramil Lundbeck, Citalopram Sandoz)	☐	☐	☐	☐	☐	☐	☐
☐ Escitalopram (incl. Cipralex Farmagon, Cipralex Lundbeck, Escitalopram Actavis)	☐	☐	☐	☐	☐	☐	☐
☐ Paroxetine (incl. Seroxat, Paroxetin Actavis, Paroxetin Farmagon)	☐	☐	☐	☐	☐	☐	☐
☐ Sertraline (incl. Sertralin HEXAL, Zoloft, Sertraline Accord)	☐	☐	☐	☐	☐	☐	☐
☐ Fluvoxamine (incl. Fevarin Mylan, Fevarin Orifarm)	☐	☐	☐	☐	☐	☐	☐
☐ Venlafaxine (incl. Efexor, Venorion, Venlazid,	☐	☐	☐	☐	☐	☐	☐

	More than 6 months before pregnancy	6 months or less before pregnancy	1st trimester	2nd trimester	3rd trimester	0 to 6 months after birth	7 to 12 months after birth
Venlafaxin Bluefish)							
☐ Duloxetine (incl. Cymbalta, Duloxetin Pensa, Duloxetine Mylan)	☐	☐	☐	☐	☐	☐	☐
☐ Mirtazapine (incl. Remeron, Mirtazapin Bluefish)	☐	☐	☐	☐	☐	☐	☐
☐ Reboxetine (incl. Edronax)	☐	☐	☐	☐	☐	☐	☐
☐ Mianserin (incl. Mianserin Mylan, Tolvon)	☐	☐	☐	☐	☐	☐	☐
☐ Amitriptyline (incl. Anafranil, Klomipramin Mylan)	☐	☐	☐	☐	☐	☐	☐
☐ Clomipramine (incl. Anafranil, Klomipramin Mylan)	☐	☐	☐	☐	☐	☐	☐
☐ Trimipramine (incl. Surmontil)	☐	☐	☐	☐	☐	☐	☐
☐ Nortriptyline (incl. Noritren)	☐	☐	☐	☐	☐	☐	☐
☐ Doxepine (inkl. Sinequan)	☐	☐	☐	☐	☐	☐	☐

63. (If yes to "I have recently given birth (in the last year)" or to "I have given birth in the last 5 years"): **Did you take antidepressant medications for your mental illness while breastfeeding?**

☐ No, never
☐ Yes, but the child received pumped milk when I took the medication(s)
☐ Yes, irrespective of the use of antidepressant(s)
☐ Yes, but I adapted the timing for breastfeeding according to the intake of the antidepressant
☐ Cannot remember

☐ Other, specify:_____

64. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **Have you purposely stopped taking your prescribed antidepressant(s) during pregnancy?**

☐ Yes ☐ No ☐ Cannot remember

65. (If yes in question 64) **Which antidepressant(s) was it?**

_____

66. If yes in question 64) **Who recommended you to avoid antidepressant in pregnancy?**

☐ Physician
☐ Midwife
☐ Pharmacy personnel
☐ Family/friends
☐ Internet
☐ Nobody, my own initiative

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years").

67. **Was the dose of your prescribed antidepressant changed during pregnancy?**

☐ Yes, increased
☐ Yes, reduced
☐ I stopped taking the medication
☐ No

68. (If yes to "I am planning a pregnancy"): **On a scale from 0 (not at all) to 10 (very effective), how effective do you think your therapy with antidepressants is in treating your illness in general?**

0 1 2 3 4 5 6 7 8 9 10

69. If yes to "I am planning a pregnancy"): **On a scale from 0 (not at all) to 10 (very effective), how effective do you think your therapy with antidepressants will be in treating your illness during a future pregnancy?**

0 1 2 3 4 5 6 7 8 9 10

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years").

70. **On a scale from 0 (not at all) to 10 (very effective), how effective do you think your therapy with antidepressants is in treating your illness in general, regardless of your current or latest pregnancy?**

0 1 2 3 4 5 6 7 8 9 10

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years").

71. **On a scale from 0 (not at all) to 10 (very effective), how effective do you think your therapy with antidepressants was/is in treating your illness during your latest or current pregnancy?**

0 1 2 3 4 5 6 7 8 9 10

(If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years").

72. **If you are taking or have been taking other medications than antidepressants for your mental illness during the period of pregnancy, please choose relevant medications from the list below, and when you were using them.**

	6 months or less before pregnancy	1st trimester	2nd trimester	3rd trimester	After birth
Paracetamol (for example Panodil, Pinex)					
Opioid analgesics (for example Paralgin forte, Tramadol)					
Lithium (Lithionit)					
Antipsychotics (for example Zyprexa, Seroquel)					
Anxiolytics (for example Valium, Sobril, Atarax)					
Sleeping medications (for example Imovane, Stilnoct, Zolpidem)					

YOUR DECISION-MAKING ABOUT ANTIDEPRESSANT TREATMENT

The next questions are about your decision-making difficulties related to use of antidepressants in the period around pregnancy. There are no right or wrong answers. We are only interested in your personal views.

73. If yes to "I am planning a pregnancy"): **Which treatment option would you prefer during a future pregnancy?**

- ☐ Pharmacological treatment with antidepressants
- ☐ Non-pharmacological treatment
- ☐ Combined non-pharmacological with antidepressants & therapy
- ☐ No treatment
- ☐ Unsure

74. (If yes to "I am pregnant" or "I have recently given birth (in the last year)" or "I have given birth in the last 5 years"). **Which treatment option do you prefer in pregnancy?**

- ☐ Pharmacological treatment with antidepressants
- ☐ Non-pharmacological treatment
- ☐ Combined non-pharmacological with antidepressants & therapy
- ☐ No treatment
- ☐ Unsure

(Applicable to both questions 73 and 74): *In this section of the questionnaire,* ***the Decisional Conflict Scale (DCS)*** *was presented (O'Connor AM. Validation of a decisional conflict scale. Med Decis Making. 1995;15(1):25-30).*

YOUR PERCEPTION OF RISK DURING PREGNANCY AND WHILE BREASTFEEDING

75. Below is a list with various medications, food and other substances. Please indicate how harmful you think they are during pregnancy and lactation on a scale from 0 to 10, where 0 corresponds to 'not harmful' and 10 to 'very harmful'. With the word "harmful", we mean in relation to child longer-term development (for example autism, motor or language development, ADHD).

	Unknown substance	0	1	2	3	4	5	6	7	8	9	10
How dangerous are these during pregnancy for your child development?	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antidepressants	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antipsychotics	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Anxiolytic benzodiazepines and sleeping drugs	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antiepileptics (e.g., valproate)												
Cranberry	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Maternal psychiatric disorder	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Alcohol (*e.g. wine, beer, spirits*)	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
How dangerous are these while breastfeeding for your child development?	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antidepressants	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antipsychotics	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Anxiolytic benzodiazepines and sleeping drugs	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Antiepileptics (e.g., valproate)												
Cranberry	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Maternal psychiatric disorder	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦
Alcohol (*e.g. wine, beer, spirits*)	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦	◦

If you have not heard before about such substance, tick 'unknown substance'.

YOUR RELATIONSHIP TO YOUR DOCTOR AND TO YOUR PARTNER DURING PREGNANCY AND YOUR ATTITUDES TO MENTAL DISORDERS

Finally, here are some questions about your relationship with your doctor and your partner, as well as your attitudes towards mental illness. There are no right or wrong answers. We are only interested in your personal views. (Tick only one cross for each line)

a) **Your relationship with your doctor and your partner:**

In this section of the questionnaire, selected items of the "**Antidepressant Compliance Questionnaire" (ACQ)** tool were presented (K. Demyttenaere, et al. Development of an antidepressant compliance questionnaire. Acta Psychiatrica Scandinavica, 2004: 110; 3. 201-207).

b) **Your attitudes towards mental disorders:**

In this section of the questionnaire, selected items of the "**Indifference to stigma"** subscale were presented (Mackenzie et al. *An Adaptation and Extension of the Attitudes Toward Seeking Professional Psychological Help*. Journal of Applied Social Psychology. *2006:* 34; 11. 2410-2433).

Thank you for your help!

Supplement 2: Additional details on Methods

Self-reported psychiatric illnesses

Overall, 10 participants planning the pregnancy did not report any psychiatric illness, and left blank the section "no mental illness". Two of these were classified as having binge eating disorder based on the DSM-IV algorithm, and were thus treated as having an eating disorder. Four reported feelings of low mood in the last month and were therefore treated as having depression. One had a history of antidepressant use and was treated as having 'other mental illness'. Three participants with pregnancy status 'planning' were excluded due to their incomplete self-report item for psychiatric illness and no proxy that could be used.

Of the participants who were pregnant or recent mothers, 49 had not completed the item for self-reporting psychiatric illness. One participant had active depressive symptoms based on the EPDS score higher than 13, and was treated as having depression. Seven participants reported having experienced low mood in the last month and were treated as having depression. Three participants had reported having lost interest or low pleasure from doing things and were treated as having had or having depression.

Procedure for the eating disorder classification

Eating disorders (EDs) were classified using an algorithm used by Bulik et al. (2007), for which diagnoses aligned with the DSM-IV diagnostic criteria. This included several eating disorder subtypes. Broadly defined anorexia nervosa (AN) was defined as meeting all DSM-IV AN criteria, except for amenorrhea, and a BMI below 18.5. Broadly defined bulimia nervosa (BN) was defined as endorsing at least weekly frequency of binge eating and purging. BN any type included either purging or binge eating, BN purging type included those who were only purging, and BN non-purging type included only non-purging. Broadly defined binge eating disorder (BED) was defined as at least weekly frequency of binge eating, but with no compensatory behaviours occurring. Eating disorder not otherwise specified, purging type (EDNOS-P) was defined as purging at least weekly, but with no binge eating occurring.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.