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Results from the Norwegian Mother, Father, Child Cohort Study

Danijela Savovic

Master Thesis in Social Pharmacy

45 credits

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http://www.duo.uio.no/

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Summary

Background

There are no clinical studies on the effectiveness of antidepressant augmentation with vitamin D or omega-3 in pregnant women with depression and/or anxiety.

Aims

The primary aim of this research project is to examine the severity of depressive and anxiety symptoms during different stages of pregnancy (early and mid) in women who continued antidepressant treatment into the early stages and initiated either omega-3 or vitamin D supplements at that time, compared to no supplement initiation. The study also examined other aspects of mental health in pregnancy, including anger and joy.

Methods

This research project is based on data from the Norwegian Mother, Father, and Child Cohort Study (MoBa), which studies disease causes among mothers and children. The study is linked to records in the Medical Birth Registry of Norway (MBRN), a national health registry collecting information about all births in Norway.

This research project primarily involved women who returned Q1 and Q3 questionnaires since these provide information about the use of antidepressants, vitamin D, and omega-3, as well as mental health instruments used to measure outcomes. Women answered questions about which vitamins or supplements they used in which period of pregnancy and for how long in intervals both before and during early pregnancy (weeks 26-9, 8-5, and 4-0 before and weeks 0-4, 5-8, 9-12, 13+ weeks during pregnancy).

In this study, we evaluated symptoms of depression and anxiety at two different time points: (i) early pregnancy, at gestation week 17-18, and (ii) mid-late pregnancy, at gestation week 30. We used two tools, the Symptoms Checklist-5 (SCL-5 and SCL-8) and The Differential Emotions Scale (DES), to measure symptoms of depression and anxiety and joy and anger emotional status as outcomes. The SCL-5 was used to examine symptoms of depression and anxiety both in early and late pregnancy (available in Q1 and Q3) and the SCL-8 in late

pregnancy only (available in Q3). We have measured exposure to both antidepressants and omega 3 / vitamin D only in Q1. We have measured the outcomes (SCL) in both Q1 and Q3. Two DES subscales on joy and anger were only available in Q3, so they were used to describe and measure levels of pleasure and anger only in late pregnancy.

A generalized linear model with robust standard errors (GLM) was used to evaluate the relationship between different outcomes and antidepressant augmentation with omega-3 or vitamin D. We presented the results as the mean difference with 95% confidence intervals (CI).

Results

After we excluded women who used omega-3 eight weeks before pregnancy and those who stopped using antidepressants during pregnancy, our study population included 500 women. 43.4% (n=217) initiated omega-3 in early pregnancy, while 56.6% (n=283) didn't. Augmentation with omega-3 was examined between weeks 0 and 13+. 71% of women used omega-3 daily, 21% 4-6 times a week, and 8% just 1-3 times a week, but the doses are unknown. In early pregnancy, 37.7% of women who continued antidepressants alone reported depressive/anxiety symptoms in Q1 with 95% CI (32.2, 43.6), while 41.2% reported symptoms among women who used omega-3 with antidepressants. 95% CI was (34.7, 48.0). In late pregnancy, 28.1% of women who continued antidepressants alone reported depressive/anxiety symptoms with 95% CI (22.9, 34.0), while 32.3% reported symptoms among women who used omega-3 with antidepressants. 95% CI was (26.2, 39.1). Compared to women who continued antidepressants alone in early pregnancy, women who initiated omega-3 in addition to antidepressants had slightly higher scores on the DES-anger subscale (crude mean difference: 0.39), slightly lower scores on the DES-joy subscale (crude mean difference: 0.27), and almost the same crude score on the SCL-5 and SCL-8 (0.05, 0.03, respectively).

Women who used antidepressants with omega-3 in early pregnancy had a more elevated risk of having clinically relevant depressive/anxiety symptoms in early (crude RR: 1.09, 95% CI (0.87,1.36)) and late pregnancy (crude RR: 1.15, 95% CI (0.87,1.52)), but the associations did not reach statistical significance.

After we excluded women who used vitamin D eight weeks before pregnancy and those who stopped using antidepressants during pregnancy, our study population included 553 women. 33.6% (n=186) initiated vitamin D in early pregnancy, while 66.4% (n=367) didn't.

Augmentation with vitamin D was examined between weeks 0 and 13+. 72% of women used vitamin D daily, 19% 4-6 times a week, and 9% just 1-3 times a week, but the doses are unknown.

In early pregnancy, 39.3% of women who continued antidepressants alone reported depressive/anxiety symptoms in Q1 with a 95% CI (34.4, 44.5). In comparison, 39.9% reported symptoms among women who used vitamin D with antidepressants. 95% CI was (32.9, 47.3). In late pregnancy, 28.6% of women who used antidepressants alone reported depressive/anxiety symptoms in Q1 with a 95% CI (24.0, 33.7), while 32.6% reported symptoms among women who used vitamin D with antidepressants. 95% CI was (26.0, 39.9).

Compared to women who continued antidepressants alone in early pregnancy, women who initiated vitamin D in addition to antidepressants had slightly lower scores on the SCL-5 (crude mean difference 0.22), on the DES-joy subscale (crude mean difference 0.33), while slightly higher scores on SCL-8 (crude mean difference 0.07) and on the DES-anger subscale (crude mean difference 0.17).

Women who used antidepressants with vitamin D in early pregnancy had a more elevated risk of having clinically relevant depressive/anxiety symptoms in early (crude RR: 1.01, 95% CI (0.81,1.27)) and late pregnancy (crude RR: 1.38, 95% CI (0.86,1.50)), but the associations did not reach statistical significance.

Conclusion

This research suggests that the use of vitamin D or omega-3 supplements, in addition to antidepressants in early pregnancy, is not associated with a reduced likelihood of depression/anxiety symptoms during pregnancy. In future research, it is necessary to determine the optimal doses of omega-3 and vitamin D supplementation with antidepressants and explore whether the timing of supplementation (early or late pregnancy) affects outcome. For an optimal effect, it is essential to take the doses of the supplements that are necessary to achieve the full effect.

Sammendrag

Bakgrunn

Det finnes ingen kliniske studier om tillegsbehandling med vitamin D eller omega-3 kan forsterke effekten av antidepressiver hos gravide kvinner med depresjon og/eller angst.

Mål

Hovedmålet med dette forskningsprosjektet er å undersøke alvorlighetsgraden av depressive og angstsymptomer under ulike stadier av svangerskapet (tidlig og midt) hos kvinner som fortsatte antidepressiv behandling i de tidlige stadiene og har startet enten omega-3 eller vitamin D tilskudd på den tiden, sammenlignet med ingen tilskuddsinitiering. Studien undersøkte også andre aspekter ved mental helse under svangerskapet, inkludert sinne og glede.

Metoder

Dette forskningsprosjektet er basert på data fra den norske kohortstudien for mor, far og barn (MoBa), som studerer sykdomsårsaker blant mødre og barn. Studien er knyttet til journaler i Medisinsk fødselsregister i Norge (MBRN), et nasjonalt helseregister som samler informasjon om alle fødsler i Norge.

Dette forskningsprosjektet involverte først og fremst kvinner som returnerte Q1 og Q3 spørreskjemaer siden disse gir informasjon om bruk av antidepressiva, vitamin D og omega-3, samt mentale helseinstrumenter som brukes til å måle utfall. Kvinner svarte på spørsmål om hvilke vitaminer eller kosttilskudd de brukte i hvilken periode av svangerskapet og hvor lenge i intervaller både før og under svangerskapet (uke 26-9, 8-5 og 4-0 før og uke 0-4, 5-8 , 9-12, 13+ uker under graviditet).

I denne studien evaluerte vi symptomer av depresjonen og angst på to forskjellige tidspunkter: (i) tidlig graviditet, ved svangerskapsuke 17-18, og (ii) midten - slutten av svangerskapet, ved svangerskapsuke 30. Vi brukte to verktøy, Symptomer Sjekkliste-5 (SCL-5 og SCL-8) og The Differential Emotions Scale (DES), for å måle symptomer på depresjon og angst og glede og sinne emosjonell status som utfall. SCL-5 ble brukt til å undersøke symptomer av depresjonen og angst både tidlig og sent i svangerskapet (tilgjengelig i Q1 og Q3) og SCL-8 kun sent i svangerskapet (tilgjengelig i Q3). Vi har målt eksponering for både antidepressiva og omega-

3 / vitamin D kun i Q1. Vi har målt utfallene (SCL) i både Q1 og Q3. To DES-underskalaer for glede og sinne var kun tilgjengelige i Q3, så de ble brukt til å beskrive og måle nivåer av glede og sinne først sent i svangerskapet.

En lineær modell med robuste standardfeil (GLM) ble brukt for å evaluere forholdet mellom ulike utfall og antidepressiv forsterkning med omega-3 eller vitamin D. Vi presenterte resultatene som gjennomsnitt verdi med 95 % konfidensintervall (CI).

Resultater

Etter at vi ekskluderte kvinner som brukte omega-3 åtte uker før svangerskapet og de som sluttet å bruke antidepressiva under svangerskapet, inkluderte vår studiepopulasjon 500 kvinner. 43.4 % (n=217) av dem startet omega-3 tidlig i svangerskapet, mens 56.6% (n=283) ikke gjorde det. Forsterkning med omega-3 ble undersøkt mellom uke 0 og 13+. 71% av kvinnene brukte omega-3 daglig, 21% 4-6 ganger i uken, og 8% bare 1-3 ganger i uken. Tidlig i svangerskapet rapporterte 37.7 % av kvinnene som fortsatte med antidepressiva alene depressive/angstsymptomer i Q1 med 95% CI (32.2, 43.6), mens 41,2% rapporterte symptomer blant kvinner som brukte omega-3 med antidepressiva. 95% CI var (34.7, 48.0). I slutten av svangerskapet rapporterte 28.1% av kvinnene som fortsatte med antidepressiva alene depressive/angstsymptomer med 95 % CI (22.9, 34.0), mens 32.3 % rapporterte symptomer blant kvinner som brukte omega-3 med antidepressiva. 95% CI var (26.2, 39.1). Sammenlignet med kvinner som fortsatte med antidepressiva alene tidlig i svangerskapet, hadde kvinner som startet omega-3 i tillegg til antidepressiva litt høyere skår på DES-anger-subskalaen (ujustert gjennomsnitt: 0.39), litt lavere skår på DES-joy-subskalaen (ujustert gjennomsnitt: 0.27), og nesten samme ujustert gjennomsnitt på SCL-5 og SCL-8 (henholdsvis 0.05, 0.03).

Kvinner som brukte antidepressiva med omega-3 tidlig i svangerskapet hadde høyere risiko for å ha klinisk relevante depressive/angstsymptomer tidlig (ujustert RR: 1.09, 95% CI (0.87, 1.36)) og sent i svangerskapet (ujustert RR: 1.15, 95% CI (0.87, 1.52)), men assosiasjonene nådde ikke signifikant nivå.

Etter at vi ekskluderte kvinner som brukte vitamin D åtte uker før graviditet og de som sluttet å bruke antidepressiva under graviditet, inkluderte vår studiepopulasjon 553 kvinner. 33.6 % (n=186) startet vitamin D tidlig i svangerskapet, mens 66,4 % (n=367) ikke gjorde det. Forsterkning med vitamin D ble undersøkt mellom uke 0 og 13+. 72% av kvinnene brukte vitamin D daglig, 19% 4-6 ganger i uken, og 9% bare 1-3 ganger i uken.

Tidlig i svangerskapet rapporterte 39.3% av kvinnene som fortsatte med antidepressiva alene depressive/angstsymptomer i Q1 med 95% CI (34.4, 44.5). Til sammenligning rapporterte 39.9% depressive symptomer blant kvinnene som brukte vitamin D sammen med antidepressiva. 95% CI var (32.9, 47.3). I slutten av svangerskapet rapporterte 28.6% av kvinnene som brukte antidepressiva alene depressive/angstsymptomer i Q1 med 95 % CI (24.0, 33,7), mens 32.6 % rapporterte symptomer blant kvinnene som brukte vitamin D sammen med antidepressiva. 95% CI var (26.0, 39.9).

Sammenlignet med kvinner som fortsatte med antidepressiva alene tidlig i svangerskapet, hadde kvinner som startet vitamin D i tillegg til antidepressiva litt lavere skår på SCL-5 (ujustert gjennomsnitt 0,22), på DES-joy subskalaen (ujustert gjennomsnitt 0,33), mens litt høyere skårer på SCL-8 (ujustert gjennomsnitt 0,07) og på DES-anger subskalaen (ujustert gjennomsnitt 0,17).

Kvinner som brukte antidepressiva med vitamin D tidlig i svangerskapet hadde forhøyet risiko for å ha klinisk relevante depressive/angst symptomer tidlig (ujustert RR: 1.01, 95% CI (0.81, 1.27)) og sent i svangerskapet (ujustert RR: 1.38, 95% CI (0.86, 1.50)), men assosiasjonene nådde ikke signifikant nivå.

Konklusjon

Denne forskningen viser at bruk av vitamin D eller omega-3 kosttilskudd, i tillegg til antidepressiva i svangerskapet, ikke er forbundet med redusert sannsynlighet for depresjon/angst symptomer under graviditet. I fremtidige forskninger er det nødvendig å finne de optimale dosene av omega-3 / vitamin D tilskudd med antidepressiva. Undersøk også om tidspunktet for tilskudd (tidlig eller sent i svangerskapet) påvirker resultatet. For en optimal effekt er det viktig å ta de dosene av kosttilskuddene som er nødvendige for å oppnå full effekt.

Foreword

This master's thesis was conducted at the Department of Pharmacy, University of Oslo, from September 2023 to April 2024. The whole period was filled with challenges, both academically and privately. Most of all, I want to thank my mentor, Prof. Angela Lupattelli, for her patience, feedback, constructive suggestions, and immense help throughout the period. I am very proud that I had the privilege to work with her and be a part of the "Pharma Safe" research group.

Furthermore, I would like to thank my colleagues from Boots Apotek for their support and understanding during this period.

Finally, I want to thank my husband, Tomislav, for his selfless support during this challenging period. I also want to thank my son Aleksa, who motivated me to practice swimming with him to stay physically and mentally healthy during several complicated months, and my daughter Sara, who filled me with positive energy with her laughter and song throughout the entire period.

Oslo, 03.04.2024

Danijela Savovic

List of definitions

Abbreviation	Definition
AD	Antidepressant
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CNS	Central nervous system
DAG	Directed acyclic graph
DES	The Differential Emotions Scale
EPDS	Edinburgh Postnatal Depression Scale
FA	Fatty acids
GBD	Global Burden of Disease
GLM	Generalized linear model
HR	Hazard ratio
IU	International unit
LBW	Low birth weight
LCPUFA	Long-chain polyunsaturated fatty acid
LGA	Large for gestational age
MBRN	The Medical Birth Registry of Norway
MDD	Major depression disorder
MoBa	The Norwegian Mother, Father, and Child Cohort Study
OAD	Other antidepressants
OR	Odds ratio
OTC	Over-the-counter drugs
Perinatal period	The ICD-10 definition is the period starting at 22 completed weeks gestation and lasting through seven days after birth.
Postpartum	The period after giving birth
PPD	Postpartum depression
PTB	Preterm birth
PUFA	Polyunsaturated fatty acids
Q1	The first quarter of a fiscal calendar or calendar year
Q3	The third quarter of a fiscal calendar or calendar year
RCT	Randomized controlled trial
RR	Risk Ratio
SCL-5 and SCL-8	Hopkins symptoms Checklist-5 and 8
SD	Standard deviation
SHI	Self-harm ideation
SNRI	Serotonin–noradrenaline reuptake inhibitors
SSRI	Selective serotonin reuptake inhibitors
TCA	Tricyclic antidepressants
TCD	Tjeneste for Sensitive Data
WHO	The World Health Organization

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1 Introduction

Relative to the Global Burden of Disease (GBD) Study conducted by the World Health Organization (WHO), unipolar major depression and anxiety are the primary causes of disease-related disability among women of reproductive age worldwide. (1) Hence, understanding the real-world effectiveness of antidepressant augmentation strategies with supplements such as vitamin D or omega-3 has important clinical implications for treatment.

1.1 Medication use in pregnancy

A substantial number of women use one or more prescription medicines during pregnancy. The most used medications are vitamins (ATC codes A11A-A11J), minerals (A12A -A12C), iron (B03A), and folic acid (B03B). (2) During the past decade, there has been an increased use of prescription medications during pregnancy in Norway, from 57% in 2005 to 62% in 2015 (3). A study from 2014 has shown that 8 of 10 women in Norway used at least one medication during pregnancy, including over-the-counter (OTC) drugs. (4) The everyday use of medication by pregnant women reflects the older maternal age at first childbirth, the increasing global burden of non-communicable diseases in women of reproductive age, and not most minor, pregnancy-specific ailments. The number of health problems among pregnant women is constantly increasing, leading to increased prescriptions of OTC medicines and herbal preparations. (5) One population-based Danish study on more than 1.3 million childbirths over 25 years found an increasing prevalence of maternal chronic disease during pregnancy, from 3.71% in 1989 to 15.76% in 2013, in all maternal age groups. (6)

Given the above, research efforts in the last decades have been focussing on the reproductive safety of commonly used medications in pregnancy. However, research on the effectiveness of pharmacological treatments in pregnancy has not been equally prioritized. Care about the use of drugs in pregnancy should focus both on the pregnant woman and the fetus. It is also essential to look at the benefits and harm to the fetus and, at the same time, safeguard maternal well-being and health. Some pregnant women do not want to use necessary medications because of fear of harming the fetus. (7) Maternal health is essential for the optimal development of the fetus. (8)

Thalidomide was indeed a powerful drug, initially hailed for its effectiveness. It was recognized as an antiemetic, meaning it helped alleviate nausea and vomiting. Thalidomide was very popular as an effective drug for morning sickness for pregnant women. Thalidomide was introduced and sold under various names across 46 countries worldwide. Precisely how many women received the drug will remain forever shrouded in uncertainty.

Only in 1961, after a rigorous investigation by two separate clinicians - Lenz in Germany and McBride in Australia - did the truth emerge: thalidomide stood as the culprit behind the most catastrophic artificial medical tragedy in history (McBride, 1961; Lenz, 1962). The consequences were astonishing, with over 10,000 children suffering from severe congenital disabilities. Additionally, during this period, there were notable reports of increased miscarriage rates. Furthermore, the thalidomide catastrophe was a groundbreaking revelation, highlighting species-specific variations in drug reactions. While mice, conventionally employed for drug testing, exhibit lower sensitivity to thalidomide, other species, such as non-human primates and rabbits, react differently.

In thalidomide embryopathy, limb damage stands out as one of the frequently observed and extensively researched characteristics. Phocomelia is the most visually arresting limb abnormality attributed to thalidomide, and it remains the archetypal representation of thalidomide embryopathy. This condition manifests as a reduction in limb length, primarily affecting the proximal elements (such as long bones), while the distal aspects (such as the hand plate) remain intact. (9)

Several studies show that women overestimate the risk of using medicines during pregnancy. Concerns and overestimation of risk related to drugs can prevent pregnant women from following essential treatments that are strictly necessary during pregnancy. In some cases, the untreated disease can be associated with a greater risk than treatment. One example of this is a study (n=4785 women aged 16-50 years) carried out to examine the suicide rate among women in and outside the perinatal period. These women had contact with mental health services during the last year before the study began. The study showed that women who committed suicide during the perinatal period were most likely to have depression (OR 2.19 [95% CI 1.43-3.34]; $p<0.001$) and were less likely to receive active treatment (OR 0.46 [0.24-0.89]; $p=0.022$) at to the time they died. (10)

Health professionals must use evidence-based information to reduce anxiety in pregnant women about the use of drugs and ensure safe treatment during pregnancy. (11) One study conducted with approximately 5,000 pregnant women and 2,000 women with infants (<25 weeks) showed that 57% of the women needed information about medicines during pregnancy. Sources they used were doctors (73%), pharmacy staff (46%), the internet (60%), midwives and nurses (33%). (12)

1.2 Mental health in pregnancy

Mental disorders are common morbidities in women of reproductive age, including during the period of pregnancy and the postnatal year. Mental disorders include several conditions, such as anxiety, depression, bipolar or eating disorders, addiction problems, psychoses, and sleep difficulties. Depression is a common complication both in the antenatal and postnatal period. (13) Although the risk factors for perinatal mental illnesses are like other periods of life, treatment in the perinatal period should be different during pregnancy and breastfeeding. While general principles of prescribing drugs in the perinatal period are provided, individual risk-benefit analyses are necessary to make informed treatment decisions. (14)

1.2.1 Prevalence of depression and anxiety in pregnancy

Untreated perinatal mental health issues have far-reaching consequences for both mothers and children, impacting their well-being and imposing substantial economic burdens on society. The prevalent mental health problem that women often face during the perinatal phase is anxiety. Despite its frequent co-occurrence with depression, researchers and health professionals have given it insufficient attention. (15)

Anxiety during pregnancy is linked to various adverse birth outcomes, and pregnant women must undergo anxiety screening and receive information about these potential risks. (16) To systematically review and meta-analysis research examining the connection between maternal anxiety during pregnancy and outcomes for both the mother and the baby in the immediate post-delivery period. (17,18)

Depression during pregnancy is a significant health problem (19), with an antenatal prevalence of 9%, which increased from 20 to 31% during the COVID period. In some populations, the percentages of anxiety and depression are 65%. (20)

One study showed that depression during pregnancy had a high risk of preterm birth (PTB) and low birth weight (LBW). A significant association was shown between depression during pregnancy and PTB (RR = 1.13; 95% CI, 1.06-1.21), while antenatal depression was significantly associated with LBW (RR= 1.18; 95% CI, 1.07-1.30). (21)

Some studies have shown an association between antenatal maternal anxiety/stress and cognitive, behavioral, and emotional problems in the child. (22)

Figure 1 shows the ICD-10 criteria, while *Figure 2* shows the DSM-5 criteria for depressive episodes.

Figure 1. ICD-10 criteria for depressive episode Copyright © 2016 Vigod et al. (23)

ICD-10 criteria for depressive episode[21]

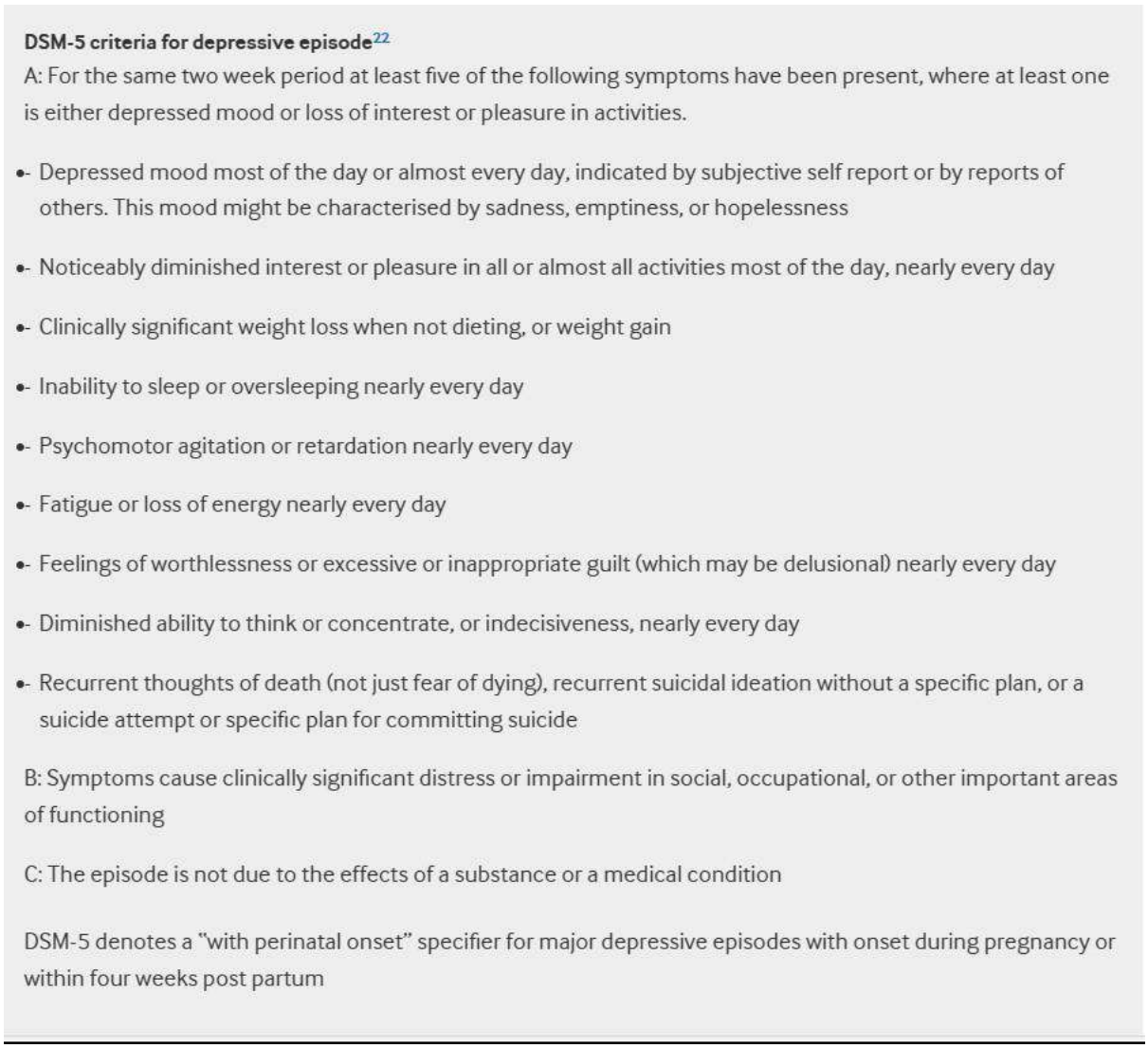
At least two weeks (but shorter periods may be reasonable if symptoms are severe and of rapid onset) of the following core symptoms experienced with severe intensity for most of every day:

- Depressed mood. The mood change is normally accompanied by an overall change in level of activity
- Loss of interest and enjoyment
- Reduced energy leading to increased fatigue and diminished activity (this also could be a physical symptom of pregnancy)

Other common symptoms:

- Reduced concentration and attention
- Reduced self esteem and self confidence
- Ideas of guilt and unworthiness
- Bleak and pessimistic views of the future
- Ideas or acts of self harm or suicide
- Disturbed sleep
- Diminished appetite

Figure 2. DSM-5 criteria for depressive episode Copyright © 2016 Vigod et al. (23)



DSM-5 criteria for depressive episode[22]

A: For the same two week period at least five of the following symptoms have been present, where at least one is either depressed mood or loss of interest or pleasure in activities.

- Depressed mood most of the day or almost every day, indicated by subjective self report or by reports of others. This mood might be characterised by sadness, emptiness, or hopelessness
- Noticeably diminished interest or pleasure in all or almost all activities most of the day, nearly every day
- Clinically significant weight loss when not dieting, or weight gain
- Inability to sleep or oversleeping nearly every day
- Psychomotor agitation or retardation nearly every day
- Fatigue or loss of energy nearly every day
- Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
- Diminished ability to think or concentrate, or indecisiveness, nearly every day
- Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or specific plan for committing suicide

B: Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C: The episode is not due to the effects of a substance or a medical condition

DSM-5 denotes a "with perinatal onset" specifier for major depressive episodes with onset during pregnancy or within four weeks post partum

1.2.2 Vitamin D

Postpartum depression (PPD) is a prevalent condition affecting a significant number of mothers. Approximately 19% of women experience depression symptoms within the first twelve weeks after giving birth, and an additional 10-20% of women experience PPD within the first year postpartum. (24) There is currently no definitive way to determine which mothers will develop depression during the perinatal period or how to prevent postpartum depression (PPD) accurately.

However, some research has shown that insufficient level of vitamin D in the body may be associated with an increased risk of developing mood, such as PPD. (25) (26)

1.2.3 Omega 3

Table 1 shows several studies have described the relationship between the omega-3 index and mental conditions. However, there is no consensus on risk stratification or target value. (27)

Table 1: Studies exploring relationships between omega-3 index and psychiatric diseases: designs and significant findings Copyright © 2023 Antao et al. (27)

Condition	Authors	Year	Study Design	Sample size	Country	Patients Population	Main O3I Outcome	Main Findings/ Conclusions
Postpartum depression	Markhus et al.	2013	cohort	35	Norway	*post partum* women	5% (cut-off)	the association between O3I and EPDS kinks at 5.1% (=QTR4) O3I was inversely associated with EPDS (R^2 = 19)
Postpartum depression	Parker et al.	2015	cohort	821 87 cases +734 controls	Australia	*post partum* women	6.6% vs. 6.8% (mean)	O3I is only slightly linked with the risk of post-natal depression (quantified by the EPDS) no significant association was found in quantification by MINIAD
Postpartum depression	Hoge et al.	2019	cohort	71 17 cases +54 controls	Belgium	*post partum* women	5% (cut-off)	women with O3I < 5% had a 5-fold increased risk of depressive episode optimal O3I cut-off was 5.08%, with a sensitivity of 53% and a specificity of 83.3%

A meta-analysis of 18 RCTs with 4,052 participants found that omega-3 polyunsaturated fatty acids (PUFAs) have a significantly small effect on perinatal depression**.** (28)

Regarding anxiety symptoms**,** a systematic review and meta-analysis of 19 RCTs involving 1,203 participants found that the combination of treatment with reduced anxiety symptoms of

omega-3 PUFAs was significantly stronger in subgroups with specific than in subgroups without specific clinical conditions. (29)

When examining the data, it was revealed that the incidence of preterm birth before 37 weeks and early preterm birth before 34 weeks was lower in women who consumed omega-3 long-chain polyunsaturated fatty acids (LCPUFA) than in women who did not. Additionally, there was potentially a lower risk of perinatal death and neonatal care admission with consumption of omega-3 LCPUFA, along with a lower risk of low birth weight (LBW) babies. However, there was also the possibility of a small increased risk of large for gestational age (LGA) babies associated with omega-3 LCPUFA consumption. (30)

1.3 Treatment of depression

1.3.1 Recommendations from the Norwegian Gynecological Association

The guide “Mental Health in Pregnancy” contains several clear and detailed recommendations on the treatment of perinatal depression:

- Women with more mental illness must be offered preconception guidance.
- Women with mild to moderate severity of depression should be offered first-line treatment, which is non-drug treatment (talk therapy, cognitive therapy, family therapy, and similar)
- It is proposed that women who have previously been exposed to violence, sexual attacks, and the like receive close follow-up from health personnel. This is because the risk of developing depression at trauma and untreated is increased, and untreated depression can lead to complications below pregnancy and at birth. (13)

Regarding drug treatment, the following recommendations apply:

- Fixed psychotropic drugs are not discontinued without consultation with the treating psychiatrist/GP.
- Drug treatment should be combined with non-drug treatment.
- Women with a high degree of severity of mental illness (e.g., depression) and who become pregnant while on medication continue the use of drugs after a thorough and thoughtful assessment of benefit-risk.
- Pregnant women with serious mental illness (e.g., depression) who have previously shown an excellent response to drug treatment (antidepressants) are offered treatment by medicines after assessment of benefit-risk.
- Switching between psychotropic drugs in women who have a severe mental condition and already use one medication should be discouraged as it can be problematic.
- The choice of pharmacotherapy should be based on its safety profile during pregnancy or on whether the therapy has previously had a good response.
- Serum concentration measurements should do monitoring of antidepressants due to pharmacokinetic changes that occur during pregnancy.
- Newborn children receive follow-up as the use of antidepressants and other psychotropic drugs can cause perinatal complications such as respiratory difficulties.
- It is recommended that women can breastfeed in most cases when using psychotropic drugs (antidepressants) (31)

The need for psychological or pharmacological treatment or a combination of these depends on the severity of depression. For mild depressive symptoms, it can be used psychological help such as "Guided self-help." “Guided self-help” is a method for systematic collaboration between patients and healthcare personnel, where the patient is responsible for implementing the measures. Research has shown that this method gives good results for several forms of mental health problems. (32)

The first choice for pregnant women with no history of previous use of antidepressants are selective serotonin reuptake inhibitors (SSRIs). (23) Sertraline and citalopram are preferred drugs. At the same time, paroxetine is not recommended due to an increased risk of cardiovascular malformations (31). If the woman is already using antidepressants before pregnancy, this treatment (even if it is with paroxetine) must be continued in consultation with the doctor. In such cases, the doctor must assess the benefit-risk and previous history of tolerance and effectiveness of antidepressants. Serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and buproprion can also be used in cases where there is a history of sound effects of these drugs or when SSRIs do not provide optimal impact. (23)

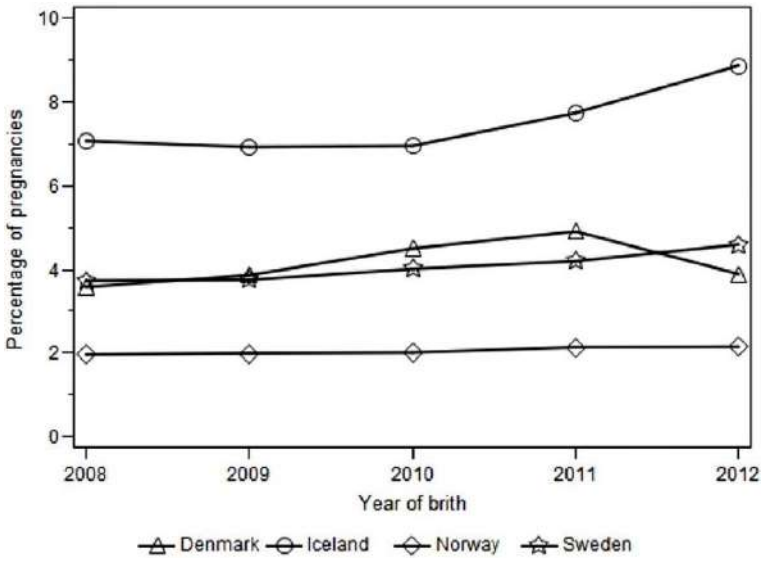
On a general basis, it is strongly recommended to continue antidepressants during pregnancy in the case of moderate-severe depression. The idea behind it is to prevent the recurrence of the disorder below pregnancy. Furthermore, switching between antidepressants during pregnancy is not recommended as there is a shortage of evidence of whether the safety profile of one drug is better than another and that the switch from one effective depression drug increases the risk of recurrence of symptoms. (23)

1.4 Use of antidepressant in pregnancy

1.4.1 Prevalence of antidepressant use in pregnancy.

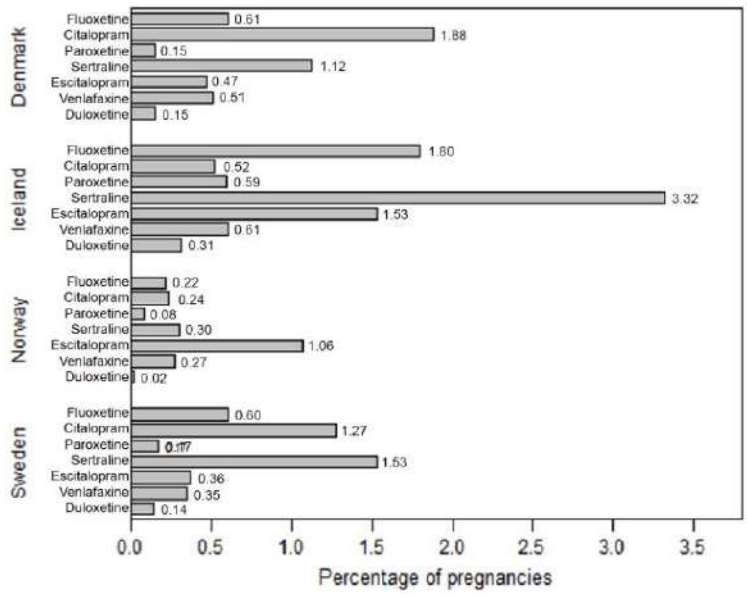
The prevalence of antidepressant use during pregnancy varies significantly across regions. According to a study, Northern America had a prevalence of 5.5%, while Europe and Australasia had prevalence estimates of 1.6% and 1.3%, respectively. (33).
A study based on nationwide data from prescription and medical birth registers in four Nordic countries from 2008 to 2012 describes the perinatal use of serotonin-noradrenaline reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs). (34)

Figure 3. Prevalence* of SSRI/SNRI use per 100 pregnancies by year of delivery and country of residence. Copyright © 2015 Zoega et al.
* at least one dispensed SSRI/SNRI during pregnancy, including 90 days period before LMP



Out of the 1.16 million pregnancies in the study population, 3.3% were exposed to SSRIs, and 0.5% were exposed to SNRIs. The overall prevalence was 3.6%**,** varying by country: 1.8% in Norway, 3.7% in Denmark and Sweden, and 7.0% in Iceland (*Figure 3)*. The highest prevalence of use occurred before pregnancy (2.7%), and this percentage gradually decreased with each passing trimester. Only 0.6% of pregnancies were exposed to these medications throughout pregnancy.

Figure 4. Prevalence* of most used SSRI/SNRI substances per 100 pregnancies by country. Copyright © 2015 Zoega et al.* at least one dispensed SSRI/SNRI during pregnancy, including the 90 days before LMP.



The most used drugs during pregnancy included sertraline**,** citalopram**,** escitalopram**,** and fluoxetine. (*Figure 4*). In Norway, the lowest rate of antidepressant use during pregnancy was observed, with an overall prevalence of 1.8%**.** Approximately 2% of women in Norway received prescriptions for SSRIs during pregnancy, while 0.3% were prescribed SNRIs. The varying prevalence of SSRI/SNRI use within the relatively homogeneous Nordic populations likely stems from differences in physicians' prescribing practices and access to non-pharmacological treatments rather than variations in underlying disease rates. Additionally, since this study relied on registry data, it remains uncertain during which trimester women consumed the prescribed medications. (35)

1.4.2 Safety of antidepressant use in pregnancy

Antidepressants (AD) can cross the placental and blood-brain barriers, which means they have the potential to affect the developing fetus's levels of monoamine neurotransmitters and possibly impact its cardiovascular, respiratory, and neurological development. (36)

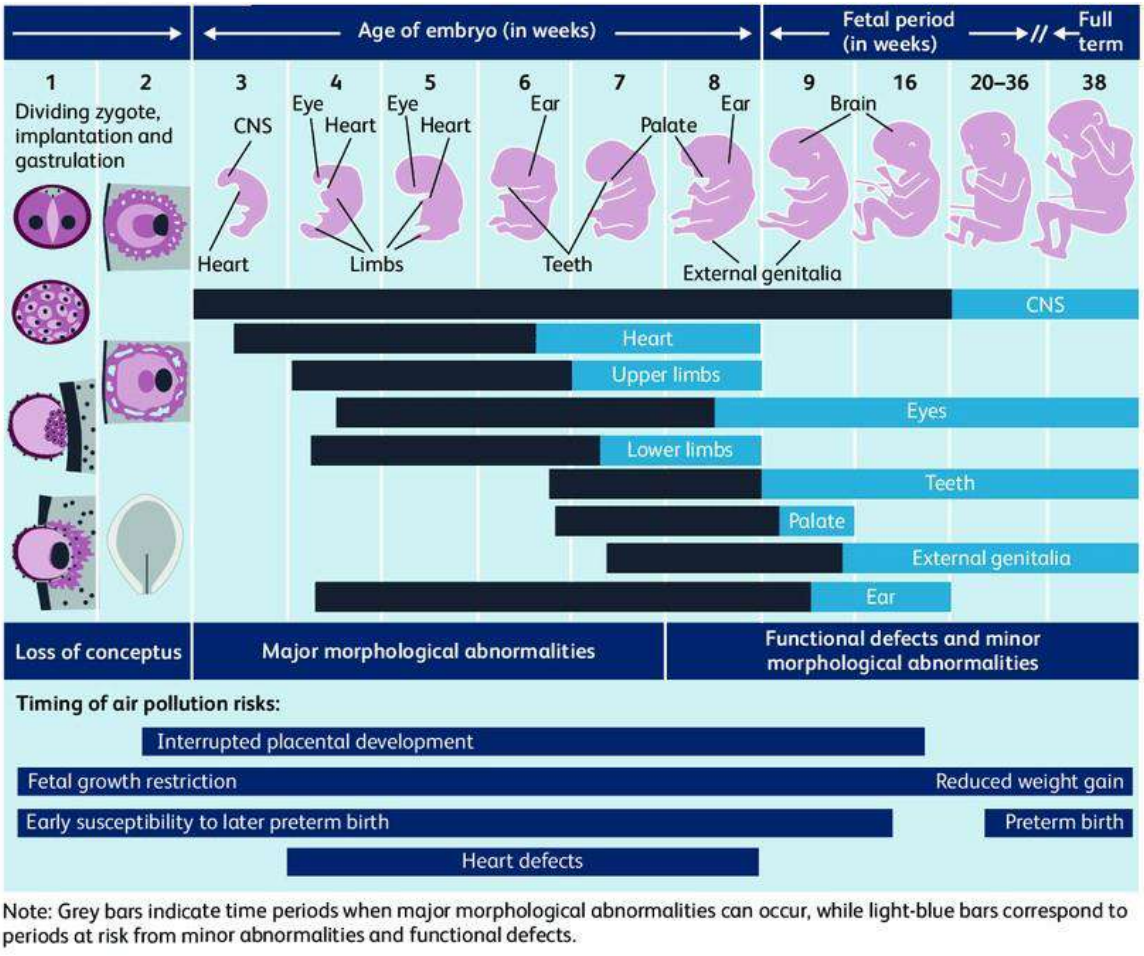
There have been many studies conducted on the use of antidepressant (AD) medication during pregnancy, and they have identified connections between such use and adverse outcomes for the mother, the fetus, and the child. However, these studies present conflicting findings, which may be attributed to variations in their ability to account for factors that may distort the results, such as underlying maternal health conditions, the severity of the disorder, genetic factors, nutritional status, concurrent medication, socio-economic disparities, or substance abuse. (33)

Most studies compare depressed individuals who receive treatment with nondepressed and nontreated control groups. It is necessary to compare the relative effects of untreated depression to depression treated with AD to correctly assess the benefits and risks of antidepressants in pregnancy. (37)

For some drugs, the pharmacokinetics can change during pregnancy due to physiological pregnancy changes (increased fluid volume, increased renal perfusion, decreased serum albumin, altered metabolic activity in the liver with faster or slower drug turnover). These changes already appear in the first trimester but are often most pronounced in the last trimester.

Not all drugs cross the placenta equally easily, but in practice, we must expect that the vast majority can reach the fetus and damage the fertilized egg or embryo up to approx. Three weeks after fertilization (approx. five weeks after the start of the last period) most often leads to abortion, while later damage can either cause abortion or a teratogenic effect. Drug use in the period immediately before conception can cause malformations if the relevant active substances are eliminated so slowly that the impact extends beyond the first part of the pregnancy. (38) (39)

Figure 5. Critical periods during fetal development



Note: Grey bars indicate time periods when major morphological abnormalities can occur, while light-blue bars correspond to periods at risk from minor abnormalities and functional defects.

Critical periods of risk from air pollution during fetal development. CNS = central nervous system.

As shown in *Figure 5*, organ formation (organogenesis) mainly occurs from 3 to 11 weeks after fertilization (5 to 13 weeks after the start of the last period). The development of the central nervous system and the heart starts early in this period. The most critical time for major skeletal malformations is from the 4th to the 6th week (somite stage). The urogenital system develops relatively late (6th to 11th week). After the organogenetic period comes a maturation phase, which for the central nervous system continues throughout pregnancy (and beyond after birth). The practical conclusion is that the risk of drug treatment of pregnant women is most significant in the first three months of fetal development, especially from the 3rd to the 11th week (from the 5th to the 13th week after the start of the last period). However, minor malformations, growth disturbances, and functional defects can occur later in pregnancy. It is not possible to

determine whether a drug causes fetal harm simply by knowing its chemical structure, mechanism of action, or passage through the placenta. Animal experiments can provide important information, but significant species differences make it challenging to conclude possible risks in humans. Perfect in vitro tests do not exist. Satisfactory epidemiological data are often lacking because obtaining controlled materials that are pure and large enough is difficult. In many cases, one only has casuistic reports to rely on. Systematic registration and follow-up of pregnancies and children can help to obtain more reliable data. However, a prerequisite for the causal relationship to be discovered and documented is, as a rule, that it is a characteristic type of malformation that is triggered with relatively high frequency. Learning and gaining an overview of the risk of exogenous substances entails potential causes of disturbances in psychological and cognitive development. Because of uncertain risk assessments, general restraint with medicines is recommended, especially in the first trimester (of course, this also applies to over-the-counter preparations). Illness can, however, entail a danger for both mother and fetus that exceeds the possible risk of the medicine's harmful effect on the fetus. Excessive caution must not lead to pregnant women being deprived of the necessary pharmacological treatment in the case of serious illnesses requiring treatment. (40)

1.4.3 Effectiveness of antidepressant treatment in pregnancy

For the mother's mental health, it is essential to treat depression and anxiety during pregnancy. Women with severe or recurrent depression who discontinue antidepressant (AD) treatment during preconception (3 months before pregnancy) or pregnancy have a higher risk of relapse (RR 2.30; 95% CI 1.58-3.35) (41).

According to a study by Cohen and colleagues, women who discontinued their medication during pregnancy had a higher risk of relapse than those who maintained their medication throughout their pregnancy. (42)

Studies have shown that women who discontinue antidepressant (AD) therapy during pregnancy have a higher risk of relapse, often with more severe symptoms. Personalized treatment and modifying the dose of antidepressants is critical to successful treatment in pregnancy, as demonstrated in a recent prospective study of pregnant women with mild to moderate depression or anxiety disorder. According to a recent prospective study of pregnant women with mild to moderate depression or anxiety disorder, modifying the dosage of antidepressants (AD) during gestation can lead to a lower prevalence of depressive symptoms in the second half of pregnancy compared to the first trimester (2.1% vs. 15.2%) (43)

According to a cross-sectional study across 12 European countries, therapy with antidepressants (AD) during pregnancy can reduce the risk of postnatal depression. (44) However, postpartum self-harm ideation (SHI), measured by item-nr 10 of the Edinburgh Postnatal Depression Scale (EPDS) in women who reported depression and anxiety during pregnancy, was found to be more elevated in women who had been using just AD. (35) (45)

Table 2: Selected studies that investigate the effectiveness of AD treatment and adherence in pregnancy on maternal mental health outcomes.

Details of the study design and population	Publication Year	Outcome measured	Main Findings
Lupattelli Angela et al. (46) population-based study based on the healthcare databases of the Lombardy region, Italy. Data were collected between 2010. and 2020. included 17,033 live-birth pregnancies within 16,091 women with antidepressant use before pregnancy	2023	Antenatal hospitalization for depression/anxiety	There were 362 (2.1 %) antenatal hospitalizations for depression/anxiety. Among the matched pairs, the cumulative incidence was 3.5 (continued antidepressant) versus 2.1 (discontinued antidepressant) per 1000 person-months, yielding a hazard ratio (HR) of 1.76 (95 % confidence interval (CI): 1.34–2.33))
Xiaoqin Liu et al. (47) score–matched cohort study. Data were collected between January 1997. and June 2016. in Denmark: women who redeemed an antidepressant prescription in the 90 days before the pregnancy. 2 matched cohorts, which matching each woman who discontinued antidepressants before pregnancy (n=2 669) or during pregnancy (n=5 467) to one who continued antidepressants based on propensity scores.	2022	Using stratified Cox regression, we estimated hazard ratios (HRs) of psychiatric emergencies in the perinatal period (pregnancy and six months postpartum).	Antidepressant discontinuation during pregnancy was associated with an increased risk of psychiatric emergency (HR =1.25, 95% CI: 1.00 to 1.55, p =0.048).
Nhung Trinh, et al. (48) Cohort study used nationwide registers in Denmark and Norway. The sample included 41 475 live-born singleton pregnancies in Denmark (1997-2016) and 16 459 in Norway (2009-2018) for women who used at least one antidepressant prescription within six months before pregnancy.	2023	Initiation of psycholeptics, psychiatric emergencies, or records of self-harm within one year postpartum	A moderately elevated probability of initiation of psycholeptics in late discontinuers (previously stable users) vs continuers was found.

1.4.4 Risks and benefits of antidepressants during pregnancy

Untreated depression during pregnancy is associated with severe adverse consequences for the fetus, such as low birth weight, premature birth, and future behavioral disturbances. (49)

A longitudinal cohort study, which included 32 women, has shown that terminating antidepressant treatment in pregnant women with a previous history of depression leads to relapse of symptoms in as many as 75% of women (even 79% in the first trimester). (50)

In the case of moderate depression, where psychological help is not sufficient or available, and in the case of severe depression, additional treatment with antidepressants must be considered. There is evidence that 50% of pregnant women with moderate-severe depression have a positive response to pharmacological treatment alone or in combination with psychological therapy. (51)

1.4.5 Effectiveness of antidepressant augmentation with omega-3 or vitamin D

A meta-analysis from 2017 is one of the first to examine the efficacy of omega-3 fatty acids as monotherapy in the acute treatment of MDD in pregnant women. (52) Results showed superior efficacy of omega-3 monotherapy over placebo with a standardized mean difference of 0.75 (95% CI=0.47, 1.04). *Table 3* presents the doses used in the analyses. It is positive that no severe side effects were registered and that all subjects completed the study. (52) (53)

Table 3: The doses of omega-3 used in the analyses

RCT	Intervention	Strategy	Control	Daily dose	Time
Kaviani *et al.* 2014	omega-3 fatty acids	Monotherapy	olive oil	1g	6 weeks
Freeman *et al.* 2008	omega-3 fatty acids	Monotherapy	corn oil+1% fish oil	1.1 g EPA+0.8 g DHA	8 weeks
Rees *et al.* 2008	omega-3 fatty acids	Monotherapy	sunola oil	0.42 g EPA. 1.64 g DHA	6 weeks
Su *et al.* 2008	omega-3 fatty acids	Monotherapy	olive oil	2.2 g EPA 1.2 g DHA	8 weeks

RCT: randomized controlled trial; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

Another meta-analysis from 2020, with 323 participants who used omega-3 FA as monotherapy and 315 participants in the placebo group, also showed that omega-3 FA had a moderate antidepressant effect compared to placebo on both pregnant and postpartum depression. Omega-3 is well tolerated. Since there are physiological differences between pregnancy and the postpartum period, the mechanisms of action are also different. This means that the effects of omega-3 on prenatal and postnatal depression were evaluated separately. Although the effects were significant in both cases, they were more evident in postpartum depression (PPD). (54)

Data from 18 RCTs of 4,052 participants showed that omega-3 supplementation had an overall small but significant helpful effect on perinatal depression compared with placebo. Due to the lack of effect, it is not recommended to prescribe omega-3 for the treatment and prevention of depressive symptoms during pregnancy. In the treatment of postpartum depression, additional treatment may be promising. (28)

A meta-analysis from 2016 found that omega-3 supplementation has a beneficial effect in patients with major depressive disorder (MDD). Notably, this effect was more pronounced in studies that used higher doses of EPA and included patients already on antidepressants. (55)

One observational study from 2023 of 165 patients evaluated the effectiveness of omega-3 fatty on symptoms of depression in patients with mild to moderate depression. Patients are divided into three groups:

1. omega-3 fatty acids alone (500mg daily),
2. antidepressant as monotherapy (escitalopram 10 mg daily, or sertraline 100 mg daily, or fluoxetine 10 mg daily),
3. A combination of antidepressants and omega-3 fatty acids (escitalopram 10 mg daily or sertraline 100 mg daily or fluoxetine 10 mg daily along with omega-3 fatty acid supplementation).

Measurements have been taken at the beginning and once a month for the next three months. The significant effect was after the second and third months. Depression symptoms improved in all groups. Patients who received antidepressants along with omega-3 showed significantly more substantial improvement in symptoms than those who received omega-3 supplementation alone or antidepressants alone. The study showed that a combination of antidepressants and omega-3 led to a reduction of depressive symptoms and recommended the use of omega-3 fatty

acids as an adjunctive therapy along with antidepressants to reduce the severity of depression. (56)

One randomized controlled trial (RCT) study for vitamin D demonstrated positive results as an additional therapy for depression. (57) Studies examining the effectiveness of dietary intervention for perinatal depression and/or anxiety in a randomized controlled trial have shown that vitamin D taken at doses of 1800–3500 IU per day may show an effect in the treatment of perinatal depression. (58)

An RCT study from 2016 was conducted on 169 pregnant women over the age of 18 who had no pregnancy complications with a depression score of 0 to 13. They were divided into two groups: a placebo and a group that received 2000 IU of vitamin D from 26-28 weeks of pregnancy until childbirth. Depression scores were assessed twice before delivery (26-28 and 38-40 weeks of gestation) and twice after delivery (4 and 8 weeks after delivery). The group receiving vitamin D had a significant reduction in scores of depression compared to the control group during late pregnancy, such as at 4-8 weeks postpartum. (59) (60)

There are no clinical studies on the effectiveness of antidepressant augmentation with vitamin D or omega-3 in pregnant women with depression and/or anxiety.

2 Aims

The primary aim of this research project is to investigate the effectiveness of antidepressant augmentation with vitamin D or omega-3 in pregnant women with depression and/or anxiety. The study is based on the Norwegian Mother, Father, and Child cohort study.

This research has the following specific aims:

1. To investigate the severity of depressive and anxiety symptoms in early and mid-pregnancy in women who continued antidepressant treatment into early pregnancy and initiated vitamin D in early pregnancy, compared to no supplement initiation.
2. To investigate the severity of depressive and anxiety symptoms in early and mid-pregnancy in women who continued antidepressant treatment into early pregnancy and initiated omega-3 in early pregnancy, compared to no supplement initiation.

3 Methods and materials

3.1 Study population and data collection

This research project is based on data from the Norwegian Mother, Father, and Child Cohort Study (MoBa), which studies disease causes among mothers and children. The study is related to records in a national health registry - the Medical Birth Registry of Norway (MBRN), that collect information about all births in Norway. The data linkage was done using each Norwegian citizen's unique personal identifier number**.**

MoBa is a population-based prospective pregnancy cohort study by the Norwegian Institute of Public Health. It aims to identify the causes of severe diseases in mothers and children. (61)

MoBa is a unique study that includes more than 114,000 children, 95,000 mothers, and 75,000 fathers. Pregnant women were recruited from across Norway between 1999 and 2008. They were recruited during a routine ultrasound examination offered publicly at 17-18 weeks of gestation.

The MoBa study collected data through three prenatal questionnaires administered at 17 weeks (Q1), 22 (Q2), and 30 weeks (Q3) of gestation. Additionally, multiple postnatal self-administered questionnaires were completed six months postpartum and at various child ages up to adolescence. Fathers completed one questionnaire at about gestational week 17. The participation rate in MoBa was 41% of the invited pregnancies. Approximately 16,400 women participated in more than one pregnancy. (62)

This research project primarily involved women who returned Q1 and Q3 questionnaires since these provide information about the use of antidepressants, vitamin D, and omega-3, as well as mental health instruments used to measure outcomes. Since the population of interest in this overall research project was pregnant women with a mental illness before and during pregnancy, the MoBa sample is only a sub-sample of the full MoBa women having the above inclusion criteria (i.e., having a mental illness before and/or during pregnancy).

3.2 Inclusion and Exclusion Criteria

The main inclusion criteria in our study were:

a. Self-reporting depressive and/or anxiety disorders before pregnancy starts. During Q1 and Q3, women were provided with a list of prior or concurrent illnesses, including depression (in both Q1 and Q3), anxiety (only in Q1), and other mental disorders (both Q1 and Q3).
b. Continued use of antidepressants from six months before pregnancy into early pregnancy, between gestational weeks 0-13. Women answered questions about which medication they used in which period of pregnancy and for how long in eight-time intervals during gestation (weeks 0-4, 5-8, 9-12, etc.). In MoBa was measured the use of antidepressants during the six months before pregnancy to identify women who stopped taking medication at the beginning of their pregnancy. We categorized drugs using the Anatomical Therapeutic Chemical (ATC) Classification System. (63) It included all selective serotonin reuptake inhibitors - SSRIs (ATC code N06AB), serotonin-noradrenaline reuptake inhibitors - SNRIs (ATC codes N06AX16 and N06AX21), tricyclic antidepressants - TCAs (ATC code N06AA), and other antidepressants (OADs) (ATC codes N06AX03, N06AX06, N06AX11, N06AX12, and N06AX18). Antidepressant exposure was defined as "any antidepressants" in pregnancy.
c. No vitamin D or omega-3 is used eight weeks before pregnancy.
d. Initiation of vitamin D or omega-3 in early pregnancy

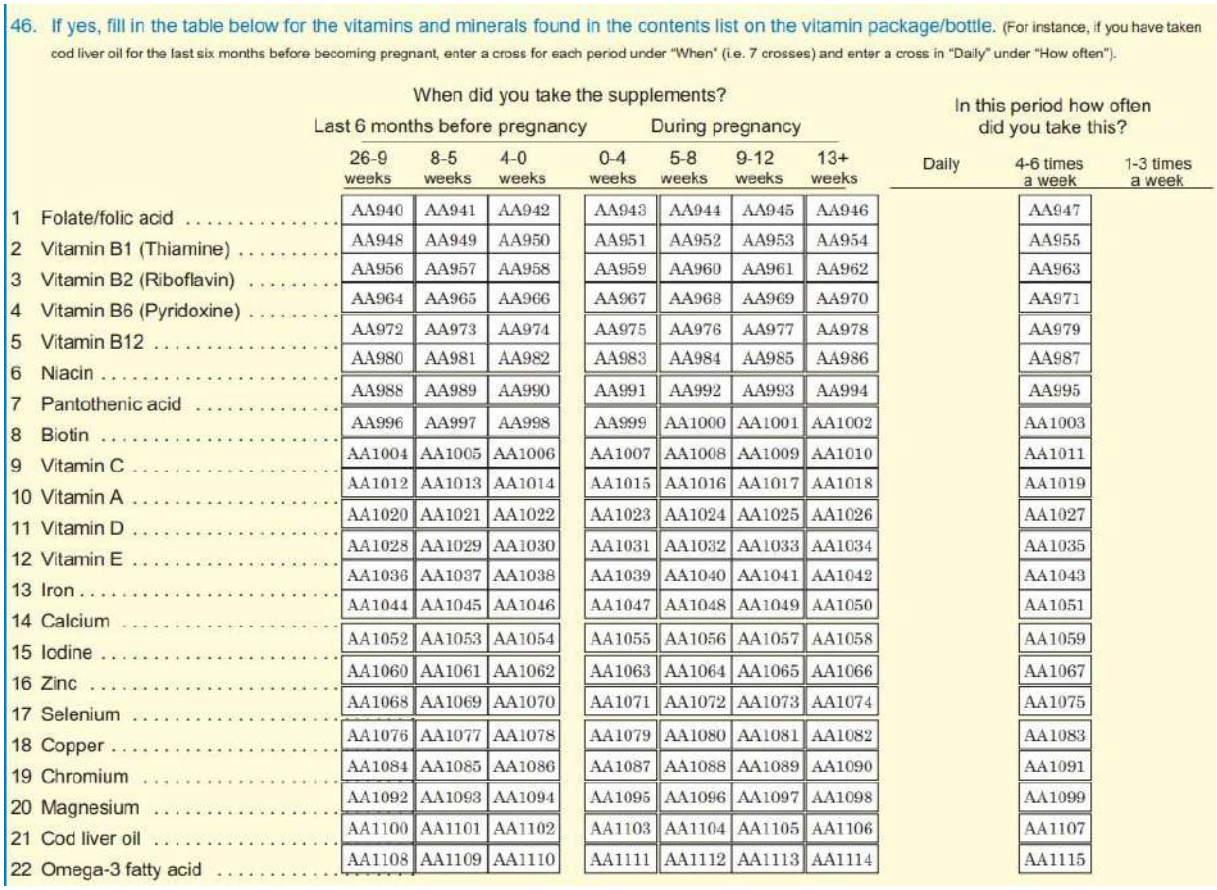
The main exclusion criteria in our study were:

a. Withdraw of the consent
b. Q3 not returned
c. Unknown timing of antidepressant exposure
d. No psychiatric disorder before pregnancy
e. Discontinued antidepressants before pregnancy
f. No antidepressant was used six months before pregnancy
g. Vitamin D, or omega-3, is used eight weeks before pregnancy.

3.3 Exposure measure: Augmentation with omega-3 or vitamin D

Information about omega-3 or vitamin D exposure timing in pregnancy was collected from MoBa Q1. Women answered questions about which vitamins or supplements they used in which period of pregnancy and for how long in intervals both before and during pregnancy (weeks 26-9, 8-5, and 4-0 before and weeks 0-4, 5-8, 9-12, 13+ weeks during pregnancy).

Figure 6. Questionnaire 1 from MoBa



46. If yes, fill in the table below for the vitamins and minerals found in the contents list on the vitamin package/bottle. (For instance, if you have taken cod liver oil for the last six months before becoming pregnant, enter a cross for each period under "When" (i.e. 7 crosses) and enter a cross in "Daily" under "How often").

	When did you take the supplements? Last 6 months before pregnancy 26-9 weeks	8-5 weeks	4-0 weeks	During pregnancy 0-4 weeks	5-8 weeks	9-12 weeks	13+ weeks	In this period how often did you take this? Daily	4-6 times a week	1-3 times a week
1 Folate/folic acid	AA940	AA941	AA942	AA943	AA944	AA945	AA946		AA947	
2 Vitamin B1 (Thiamine)	AA948	AA949	AA950	AA951	AA952	AA953	AA954		AA955	
3 Vitamin B2 (Riboflavin)	AA956	AA957	AA958	AA959	AA960	AA961	AA962		AA963	
4 Vitamin B6 (Pyridoxine)	AA964	AA965	AA966	AA967	AA968	AA969	AA970		AA971	
5 Vitamin B12	AA972	AA973	AA974	AA975	AA976	AA977	AA978		AA979	
6 Niacin	AA980	AA981	AA982	AA983	AA984	AA985	AA986		AA987	
7 Pantothenic acid	AA988	AA989	AA990	AA991	AA992	AA993	AA994		AA995	
8 Biotin	AA996	AA997	AA998	AA999	AA1000	AA1001	AA1002		AA1003	
9 Vitamin C	AA1004	AA1005	AA1006	AA1007	AA1008	AA1009	AA1010		AA1011	
10 Vitamin A	AA1012	AA1013	AA1014	AA1015	AA1016	AA1017	AA1018		AA1019	
11 Vitamin D	AA1020	AA1021	AA1022	AA1023	AA1024	AA1025	AA1026		AA1027	
12 Vitamin E	AA1028	AA1029	AA1030	AA1031	AA1032	AA1033	AA1034		AA1035	
13 Iron	AA1036	AA1037	AA1038	AA1039	AA1040	AA1041	AA1042		AA1043	
14 Calcium	AA1044	AA1045	AA1046	AA1047	AA1048	AA1049	AA1050		AA1051	
15 Iodine	AA1052	AA1053	AA1054	AA1055	AA1056	AA1057	AA1058		AA1059	
16 Zinc	AA1060	AA1061	AA1062	AA1063	AA1064	AA1065	AA1066		AA1067	
17 Selenium	AA1068	AA1069	AA1070	AA1071	AA1072	AA1073	AA1074		AA1075	
18 Copper	AA1076	AA1077	AA1078	AA1079	AA1080	AA1081	AA1082		AA1083	
19 Chromium	AA1084	AA1085	AA1086	AA1087	AA1088	AA1089	AA1090		AA1091	
20 Magnesium	AA1092	AA1093	AA1094	AA1095	AA1096	AA1097	AA1098		AA1099	
21 Cod liver oil	AA1100	AA1101	AA1102	AA1103	AA1104	AA1105	AA1106		AA1107	
22 Omega-3 fatty acid	AA1108	AA1109	AA1110	AA1111	AA1112	AA1113	AA1114		AA1115	

In *Figure 6* above, we can see which questions were answered by the women from Questionnaire 1 from MoBa. Question 46 concerns using vitamins and minerals in the 17th week of pregnancy. The women answered the questions: "When did you take the supplements?" and "In this period, how often did you take this?" The following supplements

are essential for our study: vitamin D, omega-3 fatty acids, and cod liver oil (high in omega-3 fatty acids). The following codes are used for wash-out: AA1021, AA1022 for vitamin D (8-5 and 4-0 before pregnancy, respectively) and AA1101, AA1102 for cod liver oil as well as AA1109, AA1110 for omega-3 fatty acid (8-5 and 4-0 before pregnancy, respectively). These were women who used omega-3/vitamin D eight weeks before pregnancy. The following codes are used for research: AA1023, AA1024, AA1025, AA1026 for vitamin D (0 - 13+ weeks during pregnancy) and AA1103, AA1104, AA1105, AA1106 for cod liver oil as well as AA1111, AA1112, AA1113, AA1114 for omega-3 fatty acid (0 - 13+ weeks during pregnancy). The omega-3 score is the sum of omega-3 fatty acids and cod liver oil values.

Women answer the question: “In this period, how often did you take this?”. Answers were classified as “Daily,” “4-6 times a week,” and “1-3 times a week,” which has code AA1027 for vitamin D and AA1107 and AA1115 for cod liver oil and omega-3.

3.4 Outcome measures: Maternal mental health in pregnancy

In this study, we evaluated symptoms of depression and anxiety at two different time points: (i) early pregnancy, at gestation week 17-18, and (ii) mid-late pregnancy, at gestation week 30. To measure symptoms of depression and anxiety and joy and anger emotional status as outcomes we used two tools, the Symptoms Checklist-5 (SCL-5 and SCL-8) and The Differential Emotions Scale (DES). The SCL-5 was used to examine symptoms of depression and anxiety both in early and late pregnancy (available in Q1 and Q3) and the SCL-8 in late pregnancy only (available in Q3). (64)

We have measured exposure to both antidepressants and omega-3 / vitamin D only in Q1. We have measured the outcomes (SCL) in both Q1 and Q3. Measuring in Q3 is more credible. It takes time before we see the effect of exposure. SCL-5 is measured at the same time as exposure (Q1). It shows us what conditions the women were in at the beginning of augmentation with omega-3 or vitamin D.

Two DES subscales on joy and anger were only available in Q3, so they were used to describe and measure levels of joy and anger only in late pregnancy.

The SCL-5 and SCL-8 are short versions of a validated screening instrument designed to measure symptoms of anxiety and depression, known as the Hopkins Symptom Checklist (SCL-25). (65) The SCL-25 measures symptoms related to anxiety (10 items) and depression (15 items). The SCL-25 is similar to, but not identical to, a more extended instrument, the SCL-90, which initially measures various symptoms associated with different mental disorders. (66) The SCL scale is a specifically designed psychometric tool to assess symptoms of depression in the population. It has been validated as a reliable instrument according to the ICD-10 criteria. (67)

Combinations of items in shorter versions used in MoBa testers (five of the selected items constitute SCL-5 in Q1, and eight of the items chosen to comprise the SCL-8 in Q3 and later examiners) were appointed in such a way that gave the maximum correlation between the results of the short version and the original results. Response categories were: "not at all, bothered," "a little bothered," "quite a bit bothered," and "extremely bothered," rated 1 to 4. (65) (68)

Both the SCL-5 and SCL-8 scales are represented as numeric variables, with scores ranging from 1 to 4. Higher scores on these scales indicate more severe depressive symptoms. The total score is the mean value across all five (or eight) responses. For instance, if every question is answered with 4 (indicating being "very bothered"), the total score would be calculated as (4x5)/5 = 4. A cutoff of 2 or higher predicts psychological distress. (depression and / or anxiety), while a score below 2 indicates no psychological distress. If we only look at the average value, then it is not so important to us since all women with a score of 2 or higher had symptoms of depression. That's why we looked at the yes/no scale, which informs us whether a woman has active clinical symptoms of depression or anxiety. (69) (70)

Figure 7. The (Hopkins) Symptoms Checklist-25 (HSCL-25/SCL-25) - illustration from Documentation of MoBa Instruments (65)

SCL-5	SCL-8	Have you been bothered by any of the following during the last two weeks?	Response options
1	**1**	Feeling fearful	1-Not bothered 2-A little bothered 3-Quite bothered 4-Very bothered
2	**2**	Nervousness or shakiness inside	
3	**3**	Feeling hopeless about the future	
4	**4**	Felling blue	
5	**5**	Worrying too much about things	
	6	Feeling everything is an effort	
	7	Feeling tense or keyed up	
	8	Suddenly scared for no reason	

The first analysis was done in Q1 using the SCL-5 scale of symptoms of depression and anxiety. The second analysis was done in Q3 using the SCL-5 and SCL-8 scales. The (Hopkins) Symptoms Checklist-25 (HSCL-25/SCL-25) is shown in *Figure 7* above.

Figure 8. Differential Emotional Scale (DES), Enjoyment and Anger Subscales - illustration from Documentation of MoBa Instruments (65)

	How often do you experience the following in your everyday life?	Response options
1	Feel glad about something	1-Rarely or never 2-Hardly ever 3-Sometimes 4-Often 5-Very often
2	Feel happy	
3	Feel joyful, like everything is going your way, everything is rosy	
4	Feel like screaming at somebody or banging on something	
5	Feel angry, irritated, annoyed	
6	Feel mad at somebody	

The Differential Emotional Scale - DES measures various emotions based on Izard's differential emotions theory. The scale comes in four forms. In the MoBa questionnaires, a 6-item subscale was derived from the fourth version of the DES, which consists of 12 discrete subscales (Interest, Enjoyment, Surprise, Sadness, Anger, Disgust, Contempt, Fear, Shame, Shyness, and Guilt, Hostility Inward). This subscale comprises three items related to joy and three items related to anger. Participants evaluated each item using a 5-point scale, ranging from “rarely/never” to “very often.” (62) (71)

Enjoyment and anger are fundamental emotional tendencies that are often covered in symptom assessments related to mental health. However, these emotions hold significant theoretical and empirical relevance in the context of mental disorders, overall well-being, social adaptation, interpersonal relationships, and physical health. (65)

In *Figure 8,* the response options for each DES item are rated on a 5-point scale. A score of 1 means “rarely or never,” while a score of 5 indicates “very often.” The joy and anger subscales, each containing three items, give scores ranging from 3 to 15. These scores can be averaged at the group level to describe the characteristics of the study group.

3.5 Confounding factors

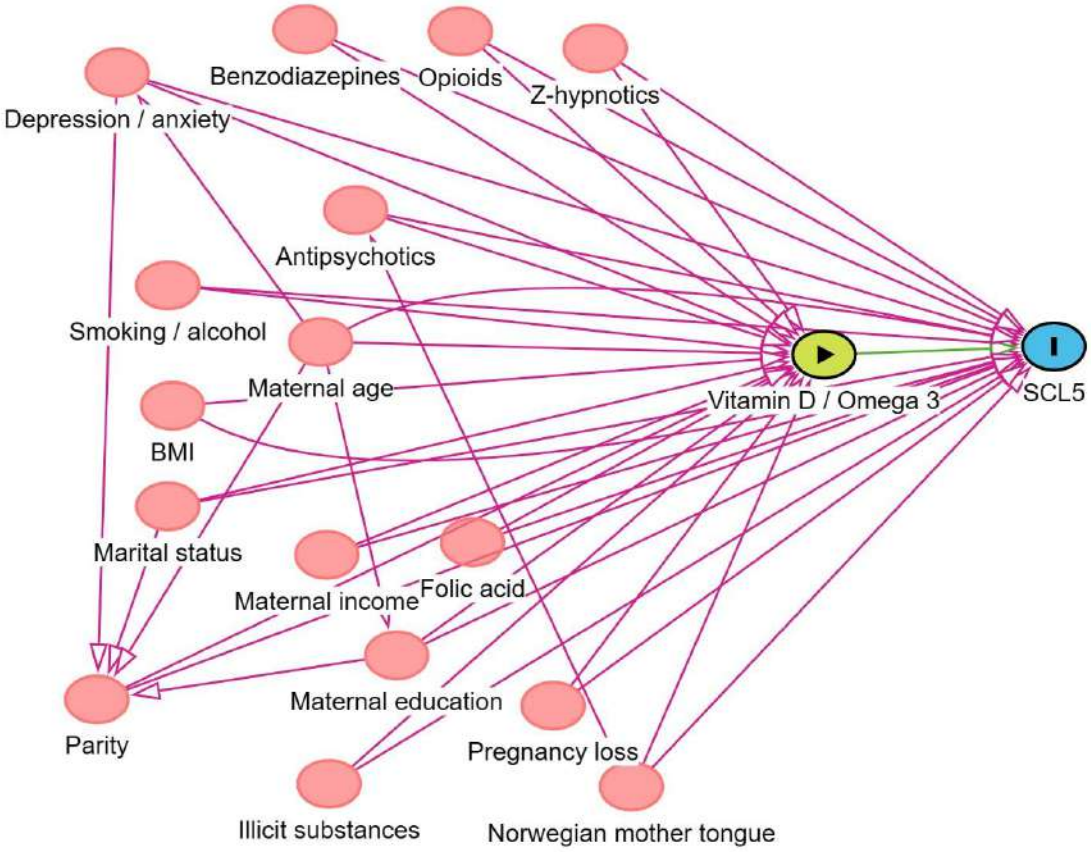


Figure 9. Directed acyclic graph (DAG) with confounding factors

We identified confounding factors by creating a directed acyclic graph (DAG) within the causal inference framework. The DAG, as shown in *Figure 9*, was constructed using Daggity (72), and the direction of arrows between variables was informed by subject knowledge and existing literature (73).

We have specifically chosen the following variables to control for confounding:

A. Sociodemographic factors

The MBRN included sociodemographic characteristics: history of pregnancy loss, maternal education, marital status, maternal age, parity, prematurity, and maternal income.

B. Lifestyle and Health Characteristics

From the MBRN, we have included the following lifestyle and health characteristics: smoking and alcohol use three months before pregnancy, BMI at conception, folic acid intake, and use of illicit substances before pregnancy.

C. Co-medication in pregnancy

Co-medication of drugs other than antidepressants used six months before pregnancy was self-reported in MoBa and included opioid analgesics (ATC code N02A), benzodiazepines (ATC codes N05B), z-hypnotics (ATC codes N05C), antipsychotics (ATC code N05A), and antiepileptics (ATC code N03A) before pregnancy.

3.6 Data analysis

3.6.1 Statistical analysis

All statistical analyses were performed using Statistical Software for Data Science (StataSE) version 18.0. Descriptive statistics were used to examine the use of antidepressants in early pregnancy and the impact of augmentation with vitamin D or omega-3.

To examine the association between augmentation of antidepressants in early pregnancy with omega 3 or vitamin D during pregnancy, the following comparison was made between the following categories:

Comparison 1: Continuers in pregnancy and augmentation with omega-3 versus continuers in pregnancy without augmentation with omega-3

Comparison 2: Continuers in pregnancy and augmentation with vitamin D versus continuers in pregnancy without augmentation with vitamin D.

A crude and adjusted generalized linear model with robust standard errors (GLM) was used to evaluate the relationship between different outcomes and antidepressant augmentation with omega-3 or vitamin D. Gaussian linear regression, which measures numeric outcomes, presents results as mean differences with a 95% confidence interval. Poisson linear regression, which measures binary outcomes (yes/ no), presents results as risk ratio (RR) with a 95% confidence interval. P-value < 0.05 was used to see the statistical significance. We used the SCL or DES score to measure outcomes between the initiators and no omega-3 or vitamin D initiators at the antidepressant continuers. The dependent variable in GLM was “any antidepressant” exposure relative to (i) initiator groups (omega-3 or vitamin D) or (ii) non-initiator groups, given the set of confounding variables (Figure 9).

3.6.2 Missing data

Over 91% of women answered all the questions about symptoms of angst/depression: SCL-5 in Q1, SCL-5 in Q3, SCL-8 in Q3, DES-joy and DES-anger from Q3 (omega-3 augmentation: 96.4%, 97.2%, 91.4%, 95.0% and 94.8%, respectively) and (vitamin D augmentation: 96.6%, 96.7%, 91.1%, 95.3% and 95.3%, respectively)

Tables 4 and *11* show the missing values (for instance, smoking, alcohol use, maternal education, maternal income, etc.)

3.7 Ethical approvals

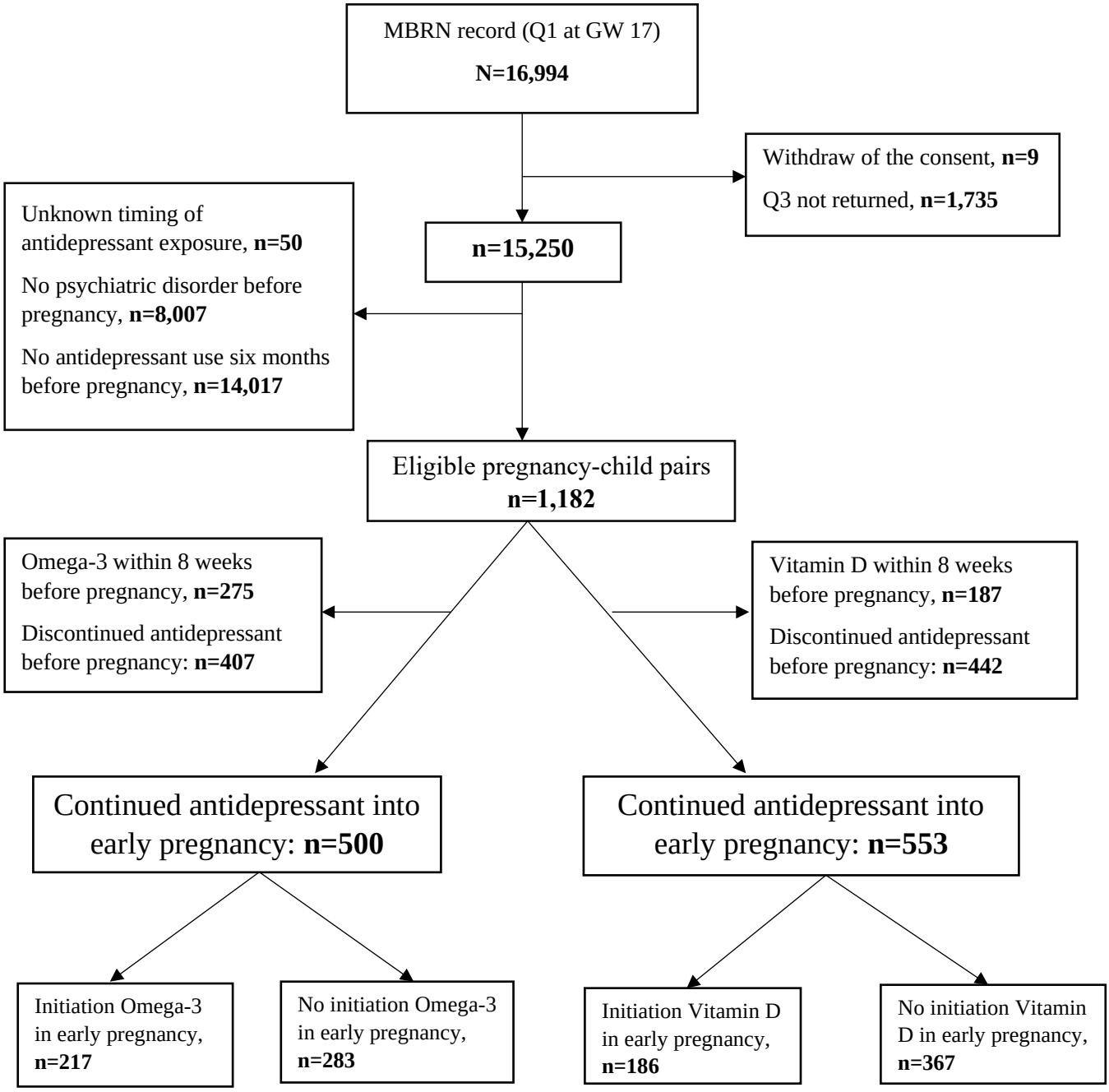
Based on the license granted by the Norwegian Data Protection Agency, data collection and the establishment of a MoBa cohort were carried out. In addition, it was approved by the Regional Committees for Medical and Health Research Ethics. The MoBa received the approval of the Regional Committees for Medical and Health Research Ethics on 12 February 2020 (reference number: 63566/REK Sør-Øst) and from the Norwegian Data Protection Agency (reference 672954).

The research was conducted using the TCD (Tjeneste for Sensitive Data) facilities, which the University of Oslo owns. These facilities are operated and developed by the TSD service group. VMware Horizon client was used for external data access and analysis. This software provides protection and control of sensitive data.

4 Results

4.1 Description of the final study population

***Figure 10*: Flow-chart to achieve the final study population**



As presented in *Figure 10,* from 16,994 pregnancies within women with valid records in the MBRN, 1,735 (10.2%) were excluded because of missing Q3, and nine were excluded because of withdrawal of consent. We excluded 50 pregnancies with unknown timing of antidepressant exposure, and 14,017 (82.5%) didn't use antidepressants six months before pregnancy. We further excluded pregnancies with ongoing use of vitamin D or omega-3 in the eight weeks preceding the start of pregnancy. Of the 1,182 eligible pregnancies with antidepressant use six months before pregnancy, we further limited the cohort to those who continued antidepressants into the first trimester of pregnancy (n=500 for the omega-3 cohort and n=553 for the vitamin D cohort). The population was further divided depending on omega 3 or vitamin D exposure augmentation in the first trimester of pregnancy.

Among 500 continuers of antidepressants (after excluding women who used omega-3 eight weeks before pregnancy and those who stopped using antidepressants during pregnancy), 217 (43.4%) women initiated omega-3 in early pregnancy. Among 553 continuers of antidepressants (after excluding women who used vitamin D eight weeks before pregnancy and those who stopped using antidepressants during pregnancy), 142 (25.7%) women initiated vitamin D in early pregnancy.

4.2 Description of the final study population - omega-3

After we excluded women who used omega-3 eight weeks before pregnancy and those who stopped using antidepressants during pregnancy, our study population included 500 women. 43.4% (n=217) initiated omega-3 in early pregnancy, while 56.6% (n=283) didn't.

Table 4 presents Descriptive Statistics by augmentation of continued antidepressants in early pregnancy with omega-3. The mean age in the study was 29.1 and 30.0 among no-initiators / initiators; the youngest woman was 18 in both groups, and the oldest was 41 years old among no-initiators and 44 among initiators.

Across the whole study, most women were in relationships (married/cohabitant) with a medium yearly income (150-399.000NOK) and had Norwegian as their mother tongue. Women who didn't initiate omega-3 in early pregnancy had a lower level of education (55.1%), had previous pregnancy (53.7), and less used folic acid before pregnancy (51.6%) relative to women who initiated omega-3 in early pregnancy: completed university/college (54.4%), primiparous (65.9%) and use folic acid (64.1%). While the percentage of women non-smokers was higher in the group who initiated omega-3 (42.9%), relative to women who didn't initiate omega-3 (36.0%), the percentage of women who used cigarettes daily was higher in the group who didn't initiate omega-3 (45.9%) relative to women who initiate omega-3 (40.6%). While women who initiated omega-3 in early pregnancy had a higher percentage of use of alcohol once per week (21.2%) vs. 10.6% at non-initiators, use of alcohol a few times per month, more than once per week was higher at no-initiators, as well as women who did not use alcohol three months before pregnancy. While women who didn't use omega-3 in early pregnancy reported more often anxiety relative to women who used (58.7% vs. 50.7%), depression was reported more in women who used omega-3 in early pregnancy (90.8% vs. 87.6%). A large percentage of both groups (more than 94%) reported that they did not use illicit substances before pregnancy. The use of other medication (opioids and benzodiazepines) six months before pregnancy was higher in the group with no initiators of omega-3, while antipsychotics were used equally (3.2%)

Table 4: Descriptive Statistics by augmentation of continued antidepressant in early pregnancy with omega-3

	No initiation of omega-3 n=283 (56.6%)		Initiation of omega-3 n=217 (43.4%)	
Obstetric risk score at baseline [mean (±SD)]	0.3	(±0.7)	0.5	(±0.9)
Maternal age at delivery [years: mean (±SD)]	29.1	(±5.0)	30.0	(±5.2)
Standardized birth weight for length and gestational age [mean (±SD)]	0.1	(±1.0)	0.0	(±1.0)
Length of gestation in days based on ultrasound estimation [mean (±SD)]	277.8	(±13.4)	276.4	(±14.2)
Maternal age				
<25	49	17.3%	26	12.0%
25-39	227	80.2%	182	83.9%
40-49	7	2.5%	9	4.1%
Marital status				
Married/Cohabitant	249	88.0%	184	84.8%
Other	34	12.0%	33	15.2%
Gross yearly income				
150-399.000NOK	172	60.8%	129	59.4%
=<150.000NOK	91	32.2%	64	29.5%
=>400.000NOK	13	4.6%	16	7.4%
Missing values	7	2.5%	8	3.7%
Completed/ongoing maternal education				
University/college	127	44.9%	118	54.4%
Lower than university/college	156	55.1%	99	45.6%
Norwegian mother tongue				
No	26	9.2%	18	8.3%
Yes	256	90.5%	196	90.3%
Missing values	<5	-	<5	-
Prematurity				
No	257	90.8%	201	92.6%
Yes	26	9.2%	16	7.4%
Parity				

	No initiation of omega-3 n=283 (56.6%)		Initiation of omega-3 n=217 (43.4%)	
Primiparous	131	46.3%	143	65.9%
Had previous pregnancies	152	53.7%	74	34.1%
History of pregnancy loss				
No	199	70.3%	150	69.1%
Yes	54	19.1%	43	19.8%
Missing values	30	10.6%	24	11.1%
Smoking three months before pregnancy				
No	102	36.0%	93	42.9%
Sometimes	29	10.2%	17	7.8%
Daily	130	45.9%	88	40.6%
Missing values	22	7.8%	19	8.8%
Alcohol three months before pregnancy.				
No	31	11.0%	17	7.8%
A few times per month	171	60.4%	121	55.8%
Once per week	30	10.6%	46	21.2%
More than once per week	29	10.2%	24	11.1%
Missing values	22	7.8%	9	4.1%
Illicit substance before pregnancy				
No	266	94%	209	96.3%
Yes	17	6%	8	3.7%
Anxiety before pregnancy				
No	117	41.3%	107	49.3%
Yes	166	58.7%	110	50.7%
Depression before pregnancy				
No	35	12.4%	20	9.2%
Yes	248	87.6%	197	90.8%
Lifetime history of major depression				
No	147	51.9%	109	50.2%
Yes	130	45.9%	105	48.4%
Missing values	6	2.1%	<5	-
Periconceptional folic acid				

	No initiation of omega-3 n=283 (56.6%)		Initiation of omega-3 n=217 (43.4%)	
No	137	48.4%	78	35.9%
Yes	146	51.6%	139	64.1%
Opioids six months before pregnancy (yes)				
Yes	9	3.2%	5	2.3%
Benzodiazepines six months before pregnancy (yes)				
Yes	26	9.2%	14	6.5%
Z-hypnotic six months before pregnancy (yes)				
Yes	0	0	<5	-
Antipsychotics six months before pregnancy (yes)				
Yes	9	3.2%	7	3.2%
Father age				
<25	23	8.1%	14	6.5%
25-39	219	77.4%	175	80.6%
40-49	37	13.1%	23	10.6%
>49	<5	-	<5	-
Missing values	<5	-	<5	-

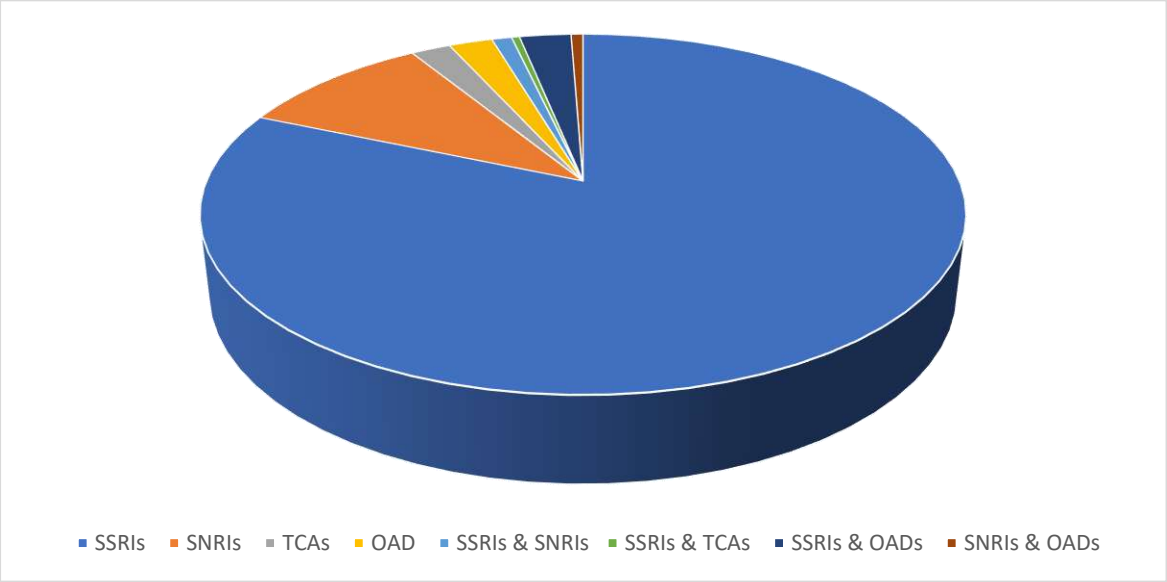
4.2.1 Exposure to antidepressants during pregnancy

The number of women who were using antidepressants during pregnancy by the time of exposure to omega-3 is more significant than 100% (*Table 5)* because women used more than 1 class of antidepressants. The majority, 477 women (95.4%), were using only 1 class of antidepressants, and 23 women (4.6%) were using two classes of antidepressants. SSRIs were the most used antidepressants, with a frequency of 85.4%. Among the non-SSRIs, the SNRIs were most frequently used (11.4%), while TCAs and OADs registered only 2.4% and 5.4%, respectively. The use of antidepressants by the timing of exposure to omega-3 is shown in *Table 5*.

Table 5: Use of antidepressants by the timing of exposure to omega-3

	n	***%***
Types of antidepressants among the antidepressant's continuers with augmentation with omega 3 (n=500)		
SSRIs	427	85.4
SNRIs	57	11.4
TCAs	12	2.4
OADs	27	5.4
	523	104.6

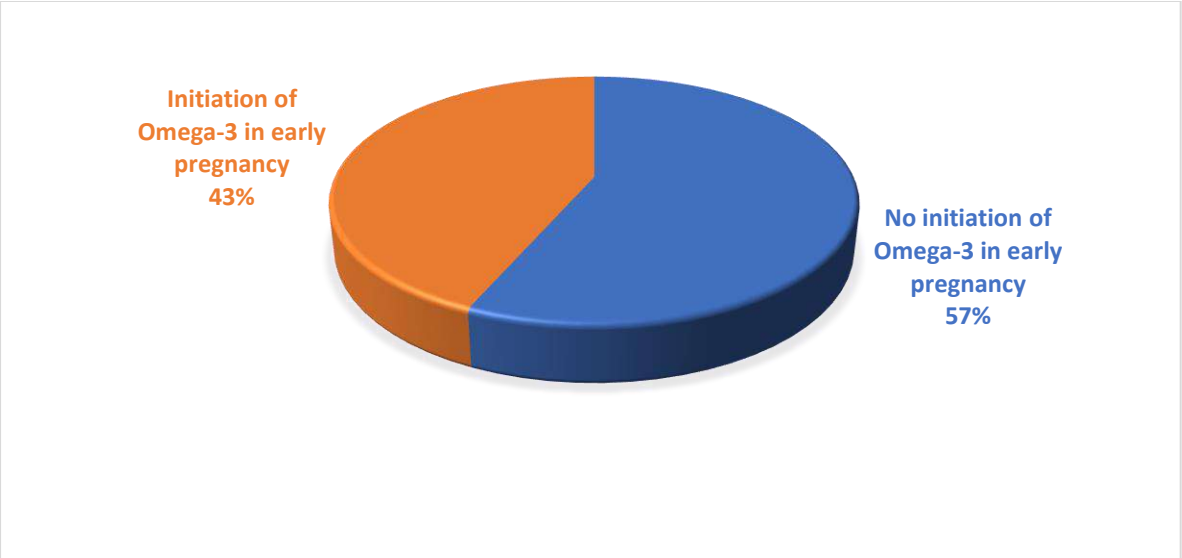
Figure 11: A type of antidepressant, such as mono and polytherapy, by the timing of exposure to omega-3 in early pregnancy



A type of antidepressant, such as mono and polytherapy, by the timing of exposure to omega-3 in early pregnancy is shown in *Figure 11*.

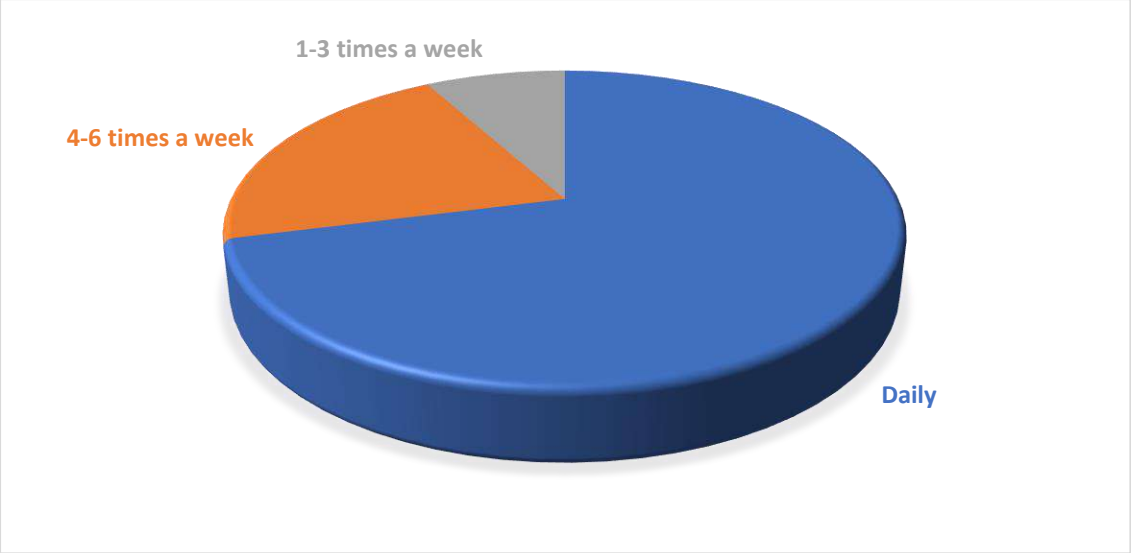
4.2.2 Augmentation with omega-3 in the final study population

Figure 12: Augmentation with omega-3 in the final study population



As shown in *Figure 12*, of the 500 women in the study population, 283 (57%) did not use omega-3 in addition to antidepressants in early pregnancy, while 217 (43%) women started with omega-3 in early pregnancy.

Figure 13: Frequency of use of omega-3 between weeks 0 and 13+



Augmentation with omega-3 was examined between weeks 0 and 13+. As shown in *Figure 13*, 71% of women used omega-3 daily, 21% 4-6 times a week, and 8% just 1-3 times a week.

4.2.3 Depressive and anxiety symptoms, joy, and anger emotions during pregnancy

In early pregnancy, as shown in *Tables 6 and 7*, 37.7% of women who continued antidepressants alone reported depressive/anxiety symptoms in Q1 with 95% CI (32.2, 43.6), while 41.2% reported symptoms among women who used omega-3 with antidepressants. 95% CI was (34.7, 48.0). The intervals overlap, meaning there is no significant difference between those groups. In late pregnancy, 28.1% of women who continued antidepressants alone reported depressive/anxiety symptoms with 95% CI (22.9, 34.0), while 32.3% reported symptoms among women who used omega-3 with antidepressants. 95% CI was (26.2, 39.1). The intervals overlap, meaning there is no significant difference between those groups.

Table 6: Depressive and anxiety symptoms during pregnancy (number/percent)

		No initiation of omega-3 in early pregnancy		**Initiation of omega-3 in early pregnancy**	
		n	**%**	**n**	**%**
Depression and/or anxiety in Q1	no	170	62.3	123	58.9
	yes	**103**	**37.7**	**86**	**41.2**
Depression and/or anxiety in Q3	no	184	71.9	136	67.7
	yes	**72**	**28.1**	**65**	**32.3**

Table 7: Depressive and anxiety symptoms during pregnancy (percent / 95% CI)

	PERCENT	**95% CI**
Depressive and anxiety symptoms (SCL-5) in early pregnancy -Q1		
No initiation of omega-3 in early pregnancy	37.7%	(32.2, 43.6)
Initiation of omega-3 in early pregnancy	41.2%	(34.7, 48.0)
Depressive and anxiety symptoms (SCL-8) in late pregnancy -Q3		
No initiation of omega-3 in early pregnancy	28.1%	(22.9, 34.0)
Initiation of omega-3 in early pregnancy	32.3%	(26.2, 39.1)

4.2.4 Association between antidepressant augmentation with omega-3 and maternal mental outcomes

Tables 8 and *9* show the association between antidepressant augmentation with omega-3 and maternal depressive and anxiety symptoms in early and late pregnancy- numeric score.

Compared to women who continued antidepressants alone in early pregnancy, women who initiated omega-3 in addition to antidepressants had slightly higher scores on the DES-anger subscale (crude mean difference: 0.39), slightly lower scores on the DES-joy subscale (crude mean difference: 0.27), and almost the same crude score on the SCL-5 and SCL-8 (0.05, 0.03, respectively). The 95% CI includes null in all crude models. It means that there is no significant effect.

Women who used omega-3 with antidepressants had a slight reduction (mean reduction: -0.13) in symptoms of depression and anxiety in late pregnancy compared to early pregnancy in the adjusted models, with a borderline 95% CI.

After adjusting for confounders shown in *Figure 9*, women who initiated omega-3 in addition to antidepressants compared to women who continued antidepressants alone in early pregnancy had higher scores on the DES-anger subscale (crude mean difference: 0.59) and SCL-5 (crude mean difference: 0.10), slightly lower scores on the DES-joy subscale (crude mean difference: 0.22). SCL-8 had almost the same adjusted score. The 95% CI includes null in SCL-5, SCL-8, and DES-joy adjusted model, which shows no significant effect. Only 95% CI to DES-anger didn’t include null. This means that there is a significant effect.

Table 8: The association between antidepressant augmentation with omega-3 and maternal depressive and anxiety symptoms in early and late pregnancy- numeric score (crude model)

CRUDE MODEL	n	mean score	Mean difference *
Depressive and anxiety symptoms (SCL-5) in early pregnancy -Q1			
No initiation of omega-3 in early pregnancy	273	1.81	0.05
Initiation of omega-3 in early pregnancy	209	1.86	
Depressive and anxiety symptoms (SCL-8) in late pregnancy -Q3			
No initiation of omega-3 in early pregnancy	256	1.76	0.03
Initiation of omega-3 in early pregnancy	201	1.79	
The difference in depressive and anxiety symptoms(SCL-5) between late and early pregnancy			
No initiation of omega-3 in early pregnancy	266	0.01	-0.05
Initiation of omega-3 in early pregnancy	202	-0.04	
Level of joy (DES-joy subscale) in late pregnancy			
No initiation of omega-3 in early pregnancy	264	10.04	-0.27
Initiation of omega-3 in early pregnancy	211	9.77	
Level of anger (DES-anger subscale) in late pregnancy			
No initiation of omega-3 in early pregnancy	264	7.27	0.39
Initiation of omega-3 in early pregnancy	210	7.66	

*Mean difference is a difference in depression and anxiety symptoms between women who continued with antidepressants and initiated omega-3 and women who used antidepressants alone

Table 9: Association between antidepressant augmentation with omega-3 and maternal depressive and anxiety symptoms in early and late pregnancy – numeric

	Crude model			Adjusted model		
OMEGA 3	**Mean difference* (95% CI)**		**p-value**	**Mean difference (95% CI)**		**p-value**
NUMERISK (Gaussian)						
Depressive and anxiety symptoms (SCL-5) in early pregnancy	0.05	(-0.08, 0.17)	0.468	0.10	(-0.04, 0.25)	0.168
Depressive and anxiety symptoms (SCL-8) in late pregnancy	0.03	(-0.08, 0.16)	0.574	0.01	(-0.12, 0.14)	0.891
The difference in depressive and anxiety symptoms (SCL-5) between late and early pregnancy	-0.05	(-0.16, 0.07)	0.414	-0.13	(-0.26, 0.01)	0.065
Level of joy (DES-joy subscale) in late pregnancy	-0.27	(-0.68, 0.14)	0.194	-0.22	(-0.69, 0.24)	0.345
Level of anger (DES-anger subscale) in late pregnancy	0.39	(-0.08, 0.85)	0.104	**0.59**	**(0.09, 1.09)**	**0.022**

Abbreviation: SCL-5-Hopkins Symptom Checklist (five items version), SCL-8-Hopkins Symptom Checklist (eight items version), CI- Confidence Interval

Adjusted model: Analyses adjusted for sociodemographic characteristics, smoking, self-reported depression, anxiety, and comedications with other psychotropic medications.

*Mean difference is a difference in depression and anxiety symptoms between women who continued with antidepressants and initiated Omega-3 and women who used antidepressants alone

Table 10 shows the association between antidepressant augmentation with omega-3 and maternal depressive and anxiety symptoms in early and late pregnancy - binary score.

Women who used antidepressants with omega-3 in early pregnancy had a more elevated risk of having clinically relevant depressive/anxiety symptoms in early (crude RR: 1.09, 95% CI (0.87,1.36)) and late pregnancy (crude RR: 1.15, 95% CI (0.87,1.52)), but the associations did not reach statistical significance.

After adjusting for confounders shown in *Figure 9*, women with continued antidepressants who initiated omega-3 in early pregnancy had a more elevated risk of having clinically relevant depressive/anxiety symptoms in early (adjusted RR: 1.16, 95% CI (0.88,1.51)) and late pregnancy (adjusted RR: 1.10, 95% CI (0.80,1.52)), but the associations did not reach statistical significance.

Table 10: Association between antidepressant augmentation with omega-3 and maternal depressive and anxiety symptoms in early and late pregnancy – binary.

	Crude model		**Adjusted model**	
OMEGA 3	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**
BINARY (Poisson)				
Depressive and anxiety symptoms (SCL-5 cut off) in early pregnancy	1.09 (0.87, 1.36)	0.445	1.16 (0.88, 1.51)	0.293
Depressive and anxiety symptoms (SCL-8 cut off) in late pregnancy	1.15 (0.87, 1.52)	0.329	1.10 (0.80, 1.52)	0.546

Abbreviation: SCL-5 cut off – yes/no depressive/anxiety symptoms in early pregnancy, SCL-8 cut off – yes/no depressive/anxiety symptoms in late pregnancy, CI- Confidence Interval; RR- relative risk.

Adjusted model: Analyses adjusted for sociodemographic characteristics, smoking, self-reported depression, anxiety, and comedications with other psychotropic medications.

4.3 Description of the final study population – vitamin D

After we excluded women who used vitamin D eight weeks before pregnancy and those who stopped using antidepressants during pregnancy, our study population included 553 women. 33.6% (n=186) initiated vitamin D in early pregnancy, while 66.4% (n=367) didn't.

Table 11 presents Descriptive Statistics by augmentation of continued antidepressants in early pregnancy with vitamin D. The mean age in the study was 30.3 and 30.0 among no-initiators / initiators; the youngest women were 18 years old, and the oldest were 44 years old in both groups.

Across the whole study, most women were in relationships (married/cohabitant) with a medium yearly income (150-399.000NOK), had higher education, and had Norwegian as their mother tongue. Women who didn't initiate vitamin D in early pregnancy had previous pregnancy (51.5%) and less used folic acid before pregnancy (52.0%) relative to women who initiated vitamin D in early pregnancy: primiparous (66.7%) and used folic acid (65.6%). While the percentage of women non-smokers and smokers was almost the same between both groups, the rate of women who used alcohol once per week was higher in the group who initiated vitamin D in early pregnancy (19.4% vs. 13.4%). Use of alcohol a few times per month, more than once per week, was higher at no-initiators, as well as women who did not use alcohol three months before pregnancy. A large percentage of both groups (more than 95%) reported that they did not use illicit substances before pregnancy.

While women who didn't use vitamin D in early pregnancy reported more often anxiety relative to women who used (55.6% vs. 52.2%), depression was reported more in women who used vitamin D in early pregnancy (90.9% vs. 87.2%). The use of benzodiazepines six months before pregnancy was higher in the group with initiators of vitamin D (8.1% vs. 6.8%, while antipsychotics in the group with no-initiators (3.5% vs. 2.7%). The use of opioids was equal (3%).

Table 11: Descriptive Statistics by augmentation of continued antidepressant in early pregnancy with vitamin D

	No initiation of vitamin D n=367 (66.4%)		Initiation of vitamin D n=186 (33.6%)	
Obstetric risk score at baseline [mean (±SD)]	0.5	(±0.9)	0.4	(±0.8)
Maternal age at delivery [years: mean (±SD)]	30.3	(±5.4)	30.0	(±4.7)
Standardized birth weight for length and gestational age [mean (±SD)]	0.03	(±1.0)	0	(±0.9)
Length of gestation in days based on ultrasound estimation [mean (±SD)]	275.2	(±14.6)	277.2	(±13.7)
Maternal age				
<25	55	15.0%	18	9.7%
25-39	296	80.7%	166	89.2%
40-49	16	4.4%	<5	-
Marital status				
Married/Cohabitant	324	88.3%	160	86.0%
Other	43	11.7%	26	14.0%
Gross yearly income				
150-399.000NOK	229	62.4%	105	56.5%
=<150.000NOK	114	31.1%	57	30.6%
=>400.000NOK	17	4.6%	16	8.6%
Missing values	7	1.9%	8	4.3%
Completed/ongoing maternal education				
University/college	185	50.4%	98	52.7%
Lower than university/college	182	49.6%	88	47.3%
Mother tongue Norwegian				
No	24	6.5%	25	13.4%
Yes	337	91.8%	160	86.0%
Missing values	6	1.6%	<5	-
Prematurity				
No	334	91.0%	169	90.9%
Yes	33	9.0%	17	9.1%

	No initiation of vitamin D n=367 (66.4%)		Initiation of vitamin D n=186 (33.6%)	
Parity				
Primiparous	178	48.5%	124	66.7%
Had previous pregnancies	189	51.5%	62	33.3%
History of pregnancy loss				
No	256	69.8%	128	68.8%
Yes	68	18.5%	38	20.4%
Missing values	43	11.7%	20	10.8%
Smoking three months before pregnancy				
No	153	41.7%	79	42.5%
Sometimes	32	8.7%	18	9.7%
Daily	156	42.5%	75	40.3%
Missing values	26	7.1%	14	7.5%
Alcohol three months before pregnancy.				
No	37	10.1%	17	9.1%
A few times per month	218	59.4%	102	54.8%
Once per week	49	13.4%	36	19.4%
More than once per week	44	12.0%	18	9.7%
Missing values	19	5.2%	13	7.0%
Illicit substances before pregnancy.				
No	353	96.2%	177	95.2%
Yes	14	3.8%	9	4.8%
Anxiety before pregnancy				
No	163	44.4%	89	47.8%
Yes	204	55.6%	97	52.2%
Depression before pregnancy				
No	47	12.8%	17	9.1%
Yes	320	87.2%	169	90.9%
Lifetime history of major depression				
No	182	49.6%	95	51.1%

	No initiation of vitamin D n=367 (66.4%)		Initiation of vitamin D n=186 (33.6%)	
Yes	179	48.8%	88	47.3%
Missing values	6	1.6%	<5	-
Periconceptional folic acid				
No	176	48.0%	64	34.4%
Yes	191	52.0%	122	65.6%
Opioids six months before pregnancy.				
Yes	11	3%	6	3.2%
Benzodiazepines six months before pregnancy.				
Yes	25	6.8%	15	8.1%
Z-hypnotic six months before pregnancy.				
Yes	<5	-	<5	-
Antipsychotics six months before pregnancy.				
Yes	13	3.5%	5	2.7%
Father age				
<25	29	7.9%	11	5.9%
25-39	281	76.6%	158	84.9%
40-49	49	13.4%	15	8.1%
>49	<5	-	<5	-
Missing values	5	1.4%	<5	-

4.3.1 Exposure to antidepressants during pregnancy

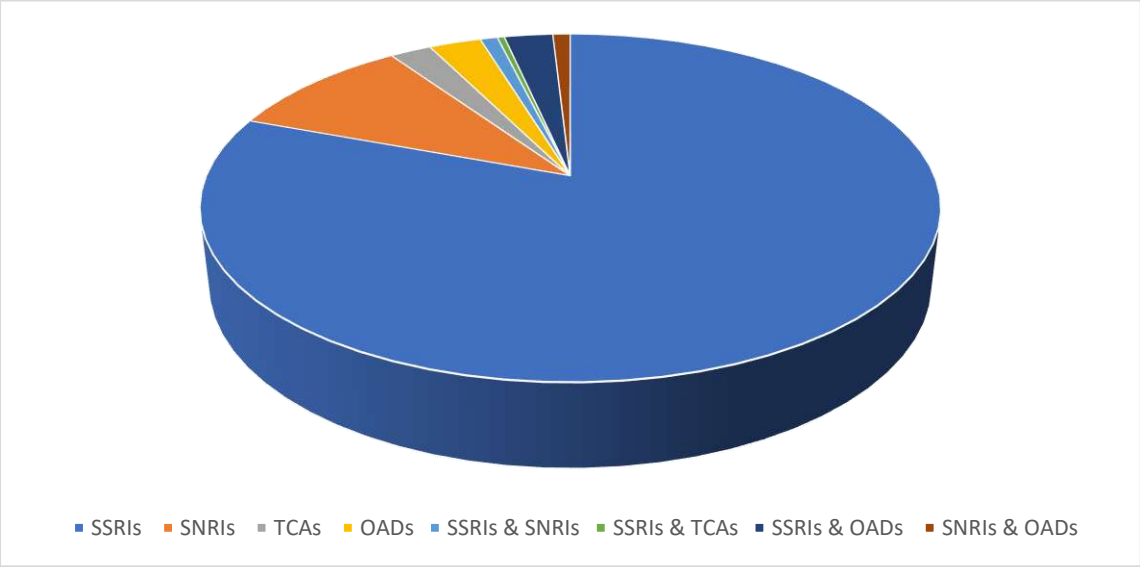
The number of women who were using antidepressants during pregnancy by the time of exposure to vitamin D is more significant than 100% (*Table 12*) because women may use more than 1 class of antidepressants. The majority, 527 women (95.3%), were using only 1 class of antidepressants, and 26 women (4.7%) were using two classes of antidepressants. SSRIs were the most used antidepressants, with a frequency of 84.4%. Among the non-SSRIs, the SNRIs were most frequently used (11.6%), while TCAs and OADs registered only 2.5% and 6.1%, respectively. The use of antidepressants by the timing of exposure to vitamin D is shown in *Table 12.*

Table 12: Use of antidepressants by the timing of exposure to vitamin D

	n	***%***
Types of antidepressants among the antidepressant continuers with augmentation with vitamin D (n=553)		
SSRIs	467	84.4
SNRIs	64	11.6
TCAs	14	2.5
OADs	34	6.1
	579	104.7

SSRIs were the most used antidepressants both six months before pregnancy and in the first trimester (with frequency from 79.9% to 44.8%). Among the non-SSRIs, the SNRIs were most frequently used (from 8.6% to 5.43%), while TCAs and OADs registered only from 2.6% to 1.2% and from 3.7% to 1.5%, respectively.

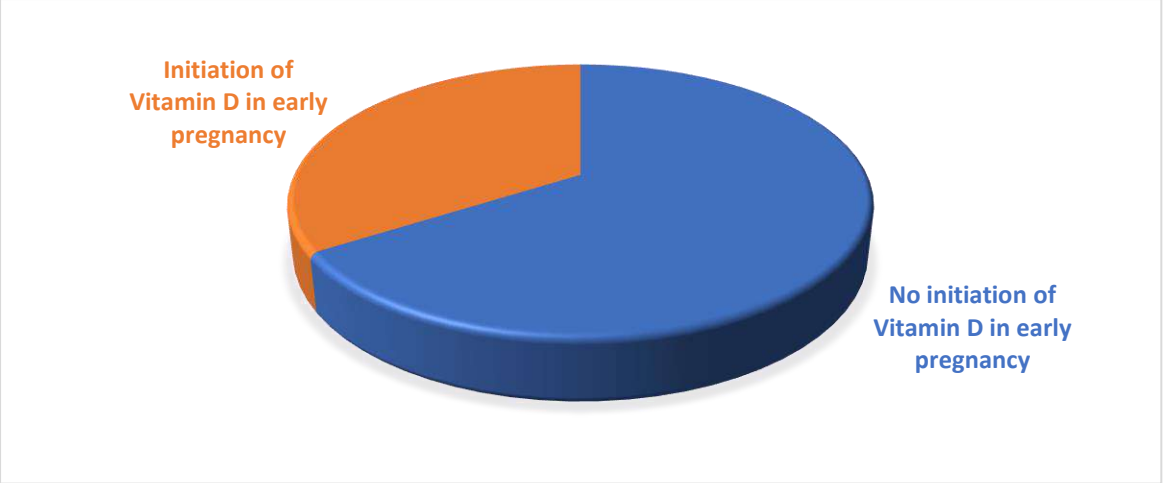
Figure 14: A type of antidepressant, such as mono and polytherapy, by the timing of exposure to vitamin D in early pregnancy



A type of antidepressant, such as mono and polytherapy, by the timing of exposure to vitamin D in early pregnancy is shown in *Figure 14*.

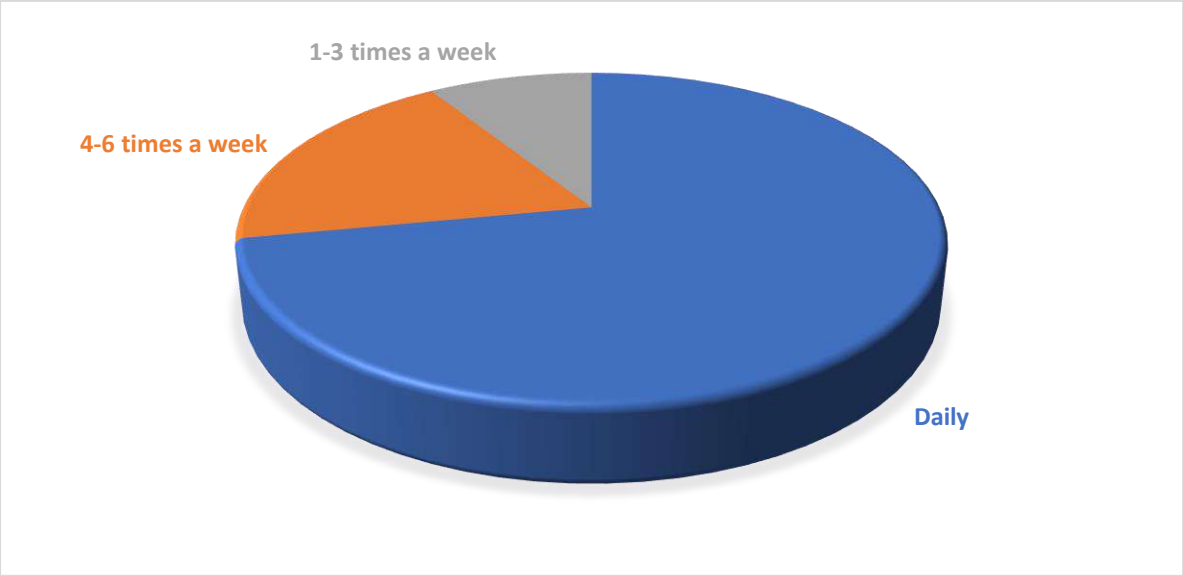
4.3.2 Augmentation with vitamin D in the Final Population

Figure 15: Augmentation with vitamin D in the final study population



As shown in *Figure 15*, of the 553 women in the study population, 367 (66%) did not use vitamin D in addition to antidepressants in early pregnancy. In contrast, 186 (34%) women started with vitamin D in early pregnancy.

Figure 16: Frequency of use of Vitamin D between weeks 0 and 13+



Augmentation with vitamin D was examined between weeks 0 and 13+. *Figure 16* shows that 72% of women used vitamin D daily, 19% 4-6 times a week, and 9% just 1-3 times a week.

4.3.3 Depressive and anxiety symptoms, joy, and anger emotions during pregnancy

In early pregnancy, as shown in *Tables 13 and 14*, 39.3% of women who continued antidepressants alone reported depressive/anxiety symptoms in Q1 with a 95% CI (34.4, 44.5). In comparison, 39.9% reported symptoms among women who used vitamin D with antidepressants. 95% CI was (32.9, 47.3). The intervals overlap, meaning there is no significant difference between those groups. In late pregnancy, 28.6% of women who used antidepressants alone reported depressive/anxiety symptoms in Q1 with a 95% CI (24.0, 33.7), while 32.6% reported symptoms among women who used vitamin D with antidepressants. 95% CI was (26.0, 39.9). The intervals overlap, too, meaning there is no significant difference between those groups.

Table 13: Depressive and anxiety symptoms during pregnancy (number and percent)

		No initiation of vitamin D in early pregnancy		Initiation of vitamin D in early pregnancy	
		n	**%**	**n**	**%**
Depression and/or anxiety in Q1	no	216	60.7	107	60.1
	yes	**140**	**39.3**	**71**	**39.9**
Depression and/or anxiety in Q3	no	237	71.4	116	67.4
	yes	**95**	**28.6**	**56**	**32.6**

Table 14: Depressive and anxiety symptoms during pregnancy (percent and 95% CI)

	PERCENT	95% CI
Depressive and anxiety symptoms (SCL-5) in early pregnancy -Q1		
No initiation of vitamin D in early pregnancy	39.3%	(34.4, 44.5)
Initiation of vitamin D in early pregnancy	39.9%	(32.9, 47.3)
Depressive and anxiety symptoms (SCL-8) in late pregnancy -Q3		
No initiation of vitamin D in early pregnancy	28.6%	(24.0, 33.7)
Initiation of vitamin D in early pregnancy	32.6%	(26.0, 39.9)

4.3.4 Association between antidepressant augmentation with vitamin D and maternal mental outcomes

Tables 15 and *16* show an association between antidepressant augmentation with vitamin D and maternal depressive and anxiety symptoms in early and late pregnancy- numeric score.

Compared to women who continued antidepressants alone in early pregnancy, women who initiated vitamin D in addition to antidepressants had slightly lower scores on the SCL-5 (crude mean difference 0.22), on the DES-joy subscale (crude mean difference 0.33), while slightly higher scores on SCL-8 (crude mean difference 0.07) and on the DES-anger subscale (crude mean difference 0.17). The 95% CI includes null in all crude models, which shows no signification.

Women who used vitamin D with antidepressants had higher symptoms of depression in late pregnancy compared to early pregnancy both in crude and adjusted models.

After adjusting for confounders shown in *Figure 9*, women who initiated vitamin D in addition to antidepressants compared to women who continued antidepressants alone in early pregnancy had higher scores on the DES-anger subscale (adjusted mean difference: 0. 28) and slightly higher scores on the SCL-8 (adjusted mean difference: 0.02), slightly lower on the DES-joy subscale (adjusted mean difference: 0.38), and slightly lower scores on the SCL-5 (adjusted mean difference: 0.02). The 95% CI includes null in all adjusted models, which shows no significant effect.

Table 15: The association between antidepressant augmentation with vitamin D and maternal depressive and anxiety symptoms in early and late pregnancy- numeric score (crude model)

	n	mean	Mean difference *
Depressive and anxiety symptoms (SCL-5) in early pregnancy -Q1			
No initiation of vitamin D in early pregnancy	356	1.85	-0.02
Initiation of vitamin D in early pregnancy	178	1.83	
Depressive and anxiety symptoms (SCL-8) in late pregnancy -Q3			
No initiation of vitamin D in early pregnancy	332	1.75	0.07
Initiation of vitamin D in early pregnancy	172	1.82	
The difference in depressive and anxiety symptoms(SCL-5) between late and early pregnancy			
No initiation of vitamin D in early pregnancy	340	-0.05	0.1
Initiation of vitamin D in early pregnancy	176	0.05	
Level of joy (DES-joy subscale) in late pregnancy			
No initiation of vitamin D in early pregnancy	349	10.12	-0.34
Initiation of vitamin D in early pregnancy	178	9.78	
Level of anger (DES-anger subscale) in late pregnancy			
No initiation of vitamin D in early pregnancy	350	7.35	0.18
Initiation of vitamin D in early pregnancy	177	7.53	

*Mean difference is a difference in depression and anxiety symptoms between women who continued with antidepressants and initiated vitamin D and women who used antidepressants alone

Table 16: Association between antidepressant augmentation with vitamin D and maternal depressive and anxiety symptoms in early and late pregnancy- numeric score

	Crude model			Adjusted model		
VITAMIN D	**Mean difference* (95% CI)**		**p-value**	**Mean difference (95% CI)**		**p-value**
NUMERISK (Gaussian)						
Depressive and anxiety symptoms (SCL-5) in early pregnancy	-0.22	(-0.15, 0.11)	0.715	-0.02	(-0.16, 0.12)	0.815
Depressive and anxiety symptoms (SCL-8) in late pregnancy	0.07	(-0.05, 0.20)	0.235	0.02	(-0.12, 0.16)	0.791
The difference in depressive and anxiety symptoms (SCL-5) between late and early pregnancy	0.10	(-0.02, 0.22)	0.108	0.03	(-0.11, 0.17)	0.664
Level of joy (DES-joy subscale) in late pregnancy	-0.33	(-0.77, 0.09)	0.124	-0.38	(-0.83, 0.08)	0.103
Level of anger (DES-anger subscale) in late pregnancy	0.17	(-0.31, 0.65)	0.482	0.28	(-0.22, 0.78)	0.278

Abbreviation: SCL-5-Hopkins Symptom Checklist (five items version), SCL-8-Hopkins Symptom Checklist (eight items version), CI- Confidence Interval

Adjusted model: Analyses adjusted for sociodemographic characteristics, smoking, self-reported depression, anxiety, and comedications with other psychotropic medications.

*Mean difference is a difference in depression and anxiety symptoms between women who continued with antidepressants and initiated Omega-3 and women who used antidepressants alone

Table 17 shows an association between antidepressant augmentation with vitamin D and maternal depressive and anxiety symptoms in early and late pregnancy - binary score.

Women who used antidepressants with vitamin D in early pregnancy had a more elevated risk of having clinically relevant depressive/anxiety symptoms in early (crude RR: 1.01, 95% CI (0.81,1.27)) and late pregnancy (crude RR: 1.38, 95% CI (0.86,1.50)), but the associations did not reach statistical significance.

After adjusting for confounders shown in *Figure 9*, women with continued antidepressants who initiated vitamin D in early pregnancy had a more elevated risk of having clinically relevant depressive/anxiety symptoms in early (adjusted RR: 1.08, 95% CI (0.84,1.39)) and late pregnancy (adjusted RR: 1.01, 95% CI (0.73-1.39)), but the associations did not reach statistical significance.

Table 17: Association between antidepressant augmentation with vitamin D and maternal depressive and anxiety symptoms in early and late pregnancy - binary score

	Crude model		**Adjusted model**	
VITAMIN D	**RR (95% CI)**	**p-value**	**RR (95% CI)**	**p-value**
BINARY (Poisson)				
Depressive and anxiety symptoms (SCL-5 cut off) in early pregnancy	1.01 (0.81, 1.27)	0.9	1.08 (0.84, 1.39)	0.539
Depressive and anxiety symptoms (SCL-8 cut off) in late pregnancy	1.38 (0.86, 1.50)	0.356	1.01 (0.73, 1.39)	0.973

Abbreviation: SCL-5 cut off – yes/no depressive/anxiety symptoms in early pregnancy, SCL-8 cut off – yes/no depressive/anxiety symptoms in late pregnancy, CI- Confidence Interval; RR- relative risk.

Adjusted model: Analyses adjusted for sociodemographic characteristics, smoking, self-reported depression, anxiety, and comedications with other psychotropic medications.

5 Discussion

5.1 Summary and interpretation of the findings

5.1.1 Omega - 3

Main findings:

- In this group of women continuing antidepressants in early pregnancy, 43% initiated omega-3 within the same period. The majority (71%) took these supplements daily.
- Initiation of omega-3 in women who continued to use antidepressants during early pregnancy was not associated with reduced symptoms of depression and anxiety relative to women who continued to use antidepressants without initiation of omega-3.
- Women who continued to use the antidepressant treatment during early pregnancy with initiation of omega-3 had higher symptoms of depression and anxiety relative to women who continued to use antidepressants alone.
- Women who used omega-3 with antidepressants had a slight reduction (mean reduction: -0.13) in symptoms of depression and anxiety in late pregnancy compared to early pregnancy in the adjusted models, with a borderline 95% CI.

These findings suggest that the use of omega-3 supplementation, in addition to antidepressants in early pregnancy, is not associated with a reduced likelihood of experiencing depressive / anxiety symptoms during pregnancy. Only adjusted anger symptoms in late pregnancy (DES-anger) had significant results.

A large percentage of women reported in early pregnancy active symptoms of depression and/or anxiety in early pregnancy (37.7% who used antidepressants alone and 41.2% of women who used antidepressants with omega-3). Later in pregnancy, that percentage decreases to 28.1% and 32.3% (women who used antidepressants alone and women who used antidepressants with omega-3, respectively). The mean value is between 1.81 (women who used antidepressants alone) and 1.86 (women who used antidepressants with omega-3) in early pregnancy and 1.76 (women who used antidepressants alone) and 1.79 (women who used

antidepressants with omega-3) in late pregnancy. These values are less than 2, which means that the population is, on average, close to the border of depression (value less than 2). The level of joy is around 10, which means that women were closer to joy (on a scale of 3-15). The level of anger is around 7. This value is closer to the lower values (on a scale of 3-15), indicating a lower anger level.

Most women (71%) used omega-3 daily. However, the main limitation is that we don't know how high a dose of omega-3 the women took. Omega-3 usually acts on depression in larger doses.

5.1.2 Vitamin D

Main findings:

- In this group of women continuing antidepressants in early pregnancy, 34% initiated vitamin D within the same period. The majority (72%) took these supplements daily.
- There was no difference in symptoms of depression and anxiety between women who continued to use antidepressants during early pregnancy and those who initiated vitamin D in addition to antidepressants.
- Women who used vitamin D with antidepressants had higher symptoms of depression in late pregnancy compared to early pregnancy both in crude and adjusted models.

These findings suggest that the use of vitamin D supplementation, in addition to antidepressants in early pregnancy, is not associated with a reduced likelihood of experiencing depressive / anxiety symptoms during pregnancy.

A large percentage of women reported in early pregnancy active symptoms of depression and/or anxiety in early pregnancy (39.3% who used antidepressants alone and 39.9% of women who used antidepressants with vitamin D). Later in pregnancy, that percentage decreases to 28.6% and 32.6% (women who used antidepressants alone and women who used antidepressants with vitamin D, respectively). The mean value is between 1.85 (women who used antidepressants alone) and 1.83 (women who used antidepressants with vitamin D) in early pregnancy and 1.75 (women who used antidepressants alone) and 1.82 (women who used antidepressants with vitamin D) in late pregnancy. These values are less than 2, which means that the population is, on average, close to the border of depression (value less than 2). The level of joy is around 10, which means that women were closer to joy (on a scale of 3-15). The

level of anger is around 7. This value is closer to the lower values (on a scale of 3-15), indicating a lower anger level.

Most women (72%) used vitamin D daily. However, the main limitation is that we don't know how high a dose of vitamin D the women took. Vitamin D usually acts on depression in larger doses.

We didn’t find the effectiveness of antidepressant augmentation either with vitamin D or omega-3 in pregnant women with depression and/or anxiety. There may be reasons for that:

- We lack information on doses, which could separate women who used lower or higher doses.
- Physiological changes occur during pregnancy, and the dose of a drug is usually necessary to adjust to that condition. The same may apply to supplements.
- These women have already used antidepressants. It may well be that they have a good effect from antidepressants alone. Then, they do not achieve a better impact with supplementary treatment subsidies.
- Since these women continue to use antidepressants during pregnancy, they have a severe level of depression. Maybe that's why neither omega-3 nor vitamin D doesn't help at that level of severity.

5.2 Strengths and limitations

The MoBa study has strengths and limitations. Data were collected prospectively, and MoBa participants were recruited voluntarily, which can lead to selection bias. Study participants may differ from the general population regarding health, lifestyle, and socioeconomic status. Study participants didn’t know the results when they reported their experiences. Although the MoBa study is significant, its participants are primarily from Norway. Therefore, the findings may not fully represent other populations or ethnic groups. Excluding genetic influences, genetics, and environmental conditions is impossible.

The study examines the mother’s health and her depressive and anxiety disorders.

An essential limitation of the study lies in the fact that maternal depressive and anxiety disorders were self-reported by participants in the MoBa dataset. Consequently, these reports are based on the maternal perception of their illness. While self-reporting is valuable for

capturing real-world experiences, it introduces the possibility of inaccuracies due to subjective interpretation or memory biases. This measurement cannot replace a clinical interview, but it still reliably shows the seriousness of the woman's condition. However, clinical assessments are necessary to understand the comprehensive mental health of the mother. The method does not accurately measure perinatal mood and anxiety.
The MoBa study specifically focused on women who had depressive/anxiety disorders at baseline. This was done to minimize the risk of the influence of other factors related to maternal health.

Over time, some participants dropped out or became unavailable for follow-up. This may affect the validity of the study. Long-term cohort studies like MoBa face logistical challenges in maintaining participant engagement and data collection over many years.

The Moba study encountered a low response rate, which may have resulted in a self-selection bias favoring the healthiest women. Researchers have diligently addressed this issue by comparing MoBa with the Norwegian birthing population. While the prevalence estimates from MoBa might not directly apply to the broader population, the associations tested within the study remain valid and informative within the context of MoBa itself.

We did not imputation missing data, which might change the results. Measuring the outcome in early pregnancy when initiating omega-3 or vitamin D is limited because women have just started using them. There was no time for it to take effect. Measuring the impact of late pregnancy is much more credible as it has had time to take effect. In our study, we don't know the dose of omega-3 or vitamin D. Only large doses are supposed to work on mental health.

5.3 Future research

5.3.1 Omega-3

Understanding the interaction between antidepressants and omega-3 during pregnancy is crucial for mental and fetal health. Further research is needed to explore these medications' potential benefits and risks, as well as the nuances and potential benefits of different treatment approaches for pregnant women experiencing these symptoms.

Because the adjusted model showed a notable association between omega-3 supplementation and increased anger symptoms, further research is needed to understand underlying mechanisms and clinical implications.

It is necessary to determine the optimal dosages of omega-3 supplementation alongside antidepressants. Explore also whether the timing of supplementation (early vs. late pregnancy) influences outcomes. Investigate the effects of combined treatment on maternal mental health beyond depression. Investigate the underlying mechanisms by which omega-3 and antidepressants interact. Consider genetic factors, maternal health conditions, overall well-being during pregnancy, and lifestyle when assessing treatment outcomes.

5.3.2 Vitamin D

This study indicates the relationship between the use of antidepressants and vitamin D. Further research may be needed to explore the potential benefits and risks of different treatment approaches during pregnancy. While the use of vitamin D alongside antidepressants may influence maternal mental health outcomes, further research is needed to understand the clinical implications fully. It is necessary to determine the optimal dosages of vitamin D supplementation alongside antidepressants. Explore also whether the timing of supplementation (early vs. late pregnancy) influences outcomes. Explore the mechanisms underlying the interaction between vitamin D and antidepressants. Consider genetic factors, maternal health conditions, and lifestyle when assessing treatment outcomes.

6 Conclusion

This research suggests that the use of vitamin D or omega-3 supplements, in addition to antidepressants in early pregnancy, is not associated with a reduced likelihood of depression/anxiety symptoms during pregnancy. In future research, it is necessary to determine the optimal doses of both omega-3 and vitamin D supplementation with antidepressants and explore whether the timing of supplementation (early or late pregnancy) affects outcome. For an optimal effect, it is essential to take the doses of the supplements that are necessary to achieve the full effect.

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