Risk factors for discontinuation of thyroid hormone replacement therapy in early pregnancy: A study from the Norwegian Mother and Child Cohort Study and the Medical Birth Registry of Norway

Risk factors for discontinuation of THRT

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Abstract

Introduction. Approximately 3% to 5% of pregnant women have hypothyroidism. Despite the potential impact of untreated hypothyroidism on infant neurodevelopment, few studies have investigated the risk factors associated with discontinuation of thyroid hormone replacement therapy (THRT) in pregnancy. We aimed to identify such factors in a population of women using THRT prior to pregnancy.

Material and methods. Data from the Norwegian Mother and Child Cohort Study were linked to records in the Medical Birth Registry of Norway. Pregnant women with hypothyroidism prior to pregnancy were categorized as discontinuers or continuers of THRT in pregnancy. The main analysis used generalized estimating equations based on multiply imputed data.

Results. Of 86 848 enrolled pregnant women, 2720 (3.2%) had a medically confirmed thyroid disorder and/or reported use of thyroid therapy. More than half (n=1587; 57.8%) used THRT prior to pregnancy; of these, 207 (13.0%) discontinued and 1380 (86.9%) continued THRT during early pregnancy. Having a non-medicated mental disorder (OR 1.64, 95% CI 1.03–2.63) and non-compliance with recommended nutritional supplementation (OR 2.51, 95% CI 1.82–3.47) increased the odds of discontinuing THRT. Women medicated for somatic comorbidities (OR 0.56, 95% CI 0.33–0.98) had a 44% decreased odds of discontinuing THRT.

Conclusions. In Norway, around 13% of women with hypothyroidism discontinue THRT in early pregnancy. For discontinuers, non-medicated mental comorbidity and non-compliance with nutritional supplements presented increased risk, while having a medicated somatic disorder was protective. Health professionals advising women with hypothyroidism should be aware of risk factors associated with THRT discontinuation.

Keywords: Drug utilization, risk factors, hypothyroidism, early pregnancy, MoBa, MBRN

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; BMI, Body Mass Index; CI, confidence interval; GEE, generalized estimating equations; LTHMD, life-time history of major depression; MBRN, Medical Birth Registry of Norway; MoBa, The

Norwegian Mother and Child Cohort Study; OR, odds ratio; *p*, *p* value; SCL-5, the short version of the Hopkins Symptom Checklist-25; THRT, thyroid hormone replacement therapy.

Key message: In early pregnancy, about 10% of pregnant women with hypothyroidism discontinue THRT. Use of patients' medical information and awareness among health professionals about the potential for suboptimal treatment of hypothyroidism in pregnancy is needed to enhance maternal and child health.

Introduction

An estimated 3% to 5% of pregnant women have hypothyroidism (1), and the prevalence estimates are similar in women of childbearing-age (2). Untreated hypothyroidism during pregnancy is associated with miscarriage and preterm delivery (3,4), and undetected and inadequate treatment of maternal thyroid deficiency during gestation is linked to lower intelligence quotient (IQ) levels in children (5). Haddow *et al*. (5) showed that 19% of children born to mothers with low thyroid hormone levels had an IQ of 85 or lower versus 5% in matched controls (5). Especially in early pregnancy, the developing fetus is highly dependent on maternal thyroid hormone (6).

A recent study in Denmark (7) reported that one in ten women with hypothyroidism discontinued thyroid hormone replacement therapy (THRT) during pregnancy. In a study by Juch *et al.* (8), 17% of women with hypothyroidism reported low adherence to THRT during pregnancy, often because of their concerns about possible teratogenic effects. Maternal neurotic traits, a failure to comply with folic acid recommendations, and the absence of a stable relationship were additional factors associated with low adherence (8).

Information about the major risk factors for THRT discontinuation remains limited, and the underlying reasons for discontinuation may be variable and depend on the study population. However, such knowledge is essential if we are to gain a better understanding of the behavioral and psychological factors that influence the use of THRT in early pregnancy.

This study investigated the predictive risk factors associated with discontinuation of THRT during early pregnancy in Norway. We hypothesized that medical as well as sociodemographic and lifestyle factors could be important drivers of THRT discontinuation.

Material and methods

The study used data from the Norwegian Mother and Child Cohort Study (MoBa) (9) and the Medical Birth Registry of Norway (MBRN) (10). Personal identification numbers allowed accurate linkage of subjects in the MoBa study with data in the MBRN registry. MoBa is a prospective, population-based cohort study of pregnancies in Norway that was initiated in 1999 by the Norwegian Institute of Public Health; follow-up is ongoing (9). From 1999 to 2008, all women in Norway were invited to participate through a invitation that also offered a routine ultrasound examination around gestational week 17. Of the invited women, around 41% consented to participate. The cohort now includes 114 500 children along with 95 200

mothers and 75 200 fathers (11). The current study is based on version 9 of the quality-assured data files that have been released for research purposes.

Data were gathered prospectively via two prenatal questionnaires that were completed at gestational week 17 (MoBa Q1) and 22 (MoBa Q2), thereby covering the first and part of the second trimester. The MoBa Q1 covers information on sociodemographic and lifestyle factors, comorbidities, reproductive history, medication use, smoking, and alcohol consumption before and during pregnancy. MoBa Q1 includes a list of concurrent and/or previous diseases, including thyroid disorders, and the responding women could indicate whether they had the disorder prior to pregnancy and/or during early pregnancy. They could also report any related use of medications as a free text entry, along with the timing of the medication use (gestational weeks 0–4, 5–8, 9–12, 13+). The MoBa Q2 questionnaire solicited information about dietary habits.

The MBRN, established in 1976, is a nationwide health registry of information about all births in Norway (10). The registry includes confirmed medical records related to maternal health before and during pregnancy and related to perinatal complications (10). The current study included pregnancies that were recorded in MBRN and that had information from the MoBa Q1 and MoBa Q2 questionnaires (n=86 848). The study only included pregnant women who reported a thyroid disorder prior to and/or during pregnancy as part of the list of diseases in MoBa Q1 and/or who had a medical record of thyroid disease in MBRN (n=2720). Information on THRT was self-reported on the MoBa Q1. Based on the Anatomical Therapeutic Chemical (ATC) Classification System (12), THRT classification included levothyroxine (ATC code H03AA01) and liothyronine (ATC code H03AA02). Figure 1 shows the criteria used to select the final study population, which comprised 1587 pregnancies of mothers who reported using THRT in the 6 months before pregnancy and who either (i) continued THRT during early pregnancy (if at least one of the 4-week intervals (0–4, 5–8, 9–12, 13+) was checked), or (ii) discontinued THRT in early pregnancy (if none of the 4-week intervals was marked). Overall, the group of continuers and discontinuers comprised 1.8% of the initial MoBa study population.

Information about sociodemographic and lifestyle factors was determined from MoBa Q1, including smoking habits, alcohol intake, education, income, body mass index (BMI) at conception, and pregnancy planning and from MBRN, including maternal age, marital status, and parity. Maternal somatic comorbidities included diabetes, arthritis, epilepsy, and

cardiovascular diseases (MBRN) and anemia (MoBa Q1). These comorbidities were classified as medicated or not medicated depending on whether the woman reported treatment for epilepsy (ATC code N03A), arthritis (L04A, N02), diabetes types I and II (A10A, A10B, A10X), anemia (B03A, B03B, B03X), or cardiovascular disorders (C01–C10) on the MoBa Q1. Mental comorbidity (depression and/or anxiety) was determined by the MoBa Q1 and was categorized as medicated or non-medicated, depending on whether the woman reported psychotropic drug use (ATC codes N05 and N06).

Depression and anxiety symptoms were measured by the short version of the Hopkins Symptom Checklist (SCL)-25 using the 5-item scale (SCL-5) in the MoBa Q1 at gestational week 17 (13). Symptoms were defined as present if the SCL-5 score was ≥ 2 (13). The life-time history of major depression (LTHMD) was measured in the MoBa Q1 by Kendler's life-time major depression scale, including five items that closely correspond to the DSM-III criteria for LTHMD (14). Reproductive history was self-reported on the MoBa Q1 and included previous pregnancy outcomes. Furthermore, within MoBa Q1, pregnant women could check a list of vitamin and mineral supplements and indicate when they had taken these. Items about the perinatal use of recommended nutritional supplements covered vitamin D, folic acid, and/or omega-3 fatty acids, either alone or in combination with additional supplements. We defined fiber intake based on the MoBa Q2, which includes several questions about the frequency and amount of vegetables, fruits, juice, and tea items that are consumed (15). The cut-off value for fiber intake was set to the median intake of 30 g fiber/day in the study population.

Statistical analyses

Generalized estimating equations (GEEs) were used to identify risk factors for discontinuation of THRT in pregnancy (16). The GEE approach was used to take into account the repeated participation of 134 women in MoBa. To build the main effect GEE model, we ran the purposeful selection (PS) algorithm (17). The PS algorithm is preferable to other selection algorithms for risk factor modeling and for epidemiological studies (17). The final multivariate GEE model was built as follows: variables were initially selected into the model based on a univariate *p* value (*p*) < 0.25. A variable was retained in the model if $p < 0.05$ or if its removal led to a change > 20% in the beta coefficients of the remaining variables (17). We present the results with crude odds ratios (ORs) and as adjusted ORs with the 95% confidence intervals (CIs). Statistical significance was defined as $p < 0.05$.

Under the assumption that data were missing at random (18), we performed multiple imputation by chained equations and imputed m=30 datasets based on the auxiliary variables initiation of delivery (i.e. spontaneous delivery, induction, or cesarean section), maternal identification number, and sex of the child, in addition to the key variables shown in Supporting Information Table S1.

Sensitivity analyses were performed to check the robustness of our findings. First, we conducted a complete case analysis. Second, we limited the cohort to one pregnancy per woman.

The GEE model was implemented with the 'xtgee' function for multiply imputed datasets in Stata (version 14) (18). For the complete case analysis, we performed the analysis in R (version 3.3.3.), applying the 'geepack' package (version 1.2-1) (16). Sensitivity analysis was performed in Stata (version 14) with the 'logistic' function for multiply imputed datasets.

Power analysis showed that we could determine the discontinuation rate of THRT of 13% with ±5% precision given a total population of n=1587 for the multiply imputed case scenarios (19).

Ethical approval

The MoBa study obtained a license from the Norwegian Data Inspectorate and approval from the Regional Committee for Medical Research Ethics (2015/1241, REK Sør-Øst B). All participants provided written informed consent prior to participation.

Results

The study population included 1453 women with hypothyroidism who had 1587 pregnancies and who reported the use of THRT prior to pregnancy. A total of 1380 (86.9%) continued THRT, while 207 (13.0%) discontinued THRT in early pregnancy. The maternal characteristics of the study population are presented in Table 1. Discontinuers were more often younger and more often smokers in early pregnancy than continuers and were less likely to take the recommended nutritional supplements or co-medications for somatic and mental comorbidities (Table 1). In addition, discontinuers had a lower educational level, lower socioeconomic status, and had less often planned the pregnancy (Table 1). A total of 14% of the population had missing data for one or several measures. Discontinuers had more missing values for specific key variables compared to continuers (Table 1).

Several factors were significantly associated with discontinuation of THRT in early pregnancy (Table 2). Women who were medicated for somatic comorbidities during early pregnancy had a 44% reduced odds of discontinuing THRT compared to women with no somatic disorders. In contrast, women who were non-medicated for treatment of mental disorders had a 64% increased odds of discontinuing THRT compared with women with no such disorder. Women who were not compliant with taking recommended nutritional supplements had a 2.5-fold increased likelihood of discontinuing THRT. The odds for discontinuation were higher in smokers and women with negative reproductive history, although these associations were borderline significant (Table 2).

In the complete case analysis (n=1362), non-compliance with nutritional supplements led to a 2.3-fold increase in the likelihood of discontinuing THRT (OR 2.31, 95% CI 1.63–3.27), while smoking doubled this likelihood (OR 2.03, 95% CI 1.16–3.56). Unlike the multiply imputed results, co-medication for somatic and mental comorbidities was not associated with THRT discontinuation. Results from the sensitivity analysis, which was restricted to 1453 pregnancies, were predominantly consistent with the results of the main analysis, except for smoking (OR 1.60, 95% CI 1.00–2.85).

Discussion

To our knowledge, this study is the first to identify risk factors for discontinuation of THRT during early pregnancy and to assess the discontinuation rate in Norway. It found that 13.0% of women with diagnosed hypothyroidism prior to pregnancy did not take THRT in early pregnancy. Although this estimate of discontinuation is not remarkably high, it raises concerns about the potential of suboptimal therapy for hypothyroidism during early pregnancy in Norway. This is important, given the adverse health implications for maternal and child health that are associated with untreated hypothyroidism (5,6). The 1.8% prevalence estimate of hypothyroidism in our study population is comparable to the rates of overt hypothyroidism reported by the study by Diéguez *et al.* (20) in which 1.9% of the study participants had overt hypothyroidism in early pregnancy.

Furthermore, the proportion of women who discontinued THRT, as well as the group characteristics of the continuers and discontinuers in the present study, was similar to that reported by Gidén *et al*. (7). In the crude comparison, discontinuers more often had an unplanned pregnancy than did continuers (24.6% vs. 17.7%). This could be because women who planned to conceive had better and more tailored preconception counselling regarding

the importance of continuing THRT in their pregnancy. Notably, this difference was no longer significant after accounting for other maternal correlates, such as smoking or education. This suggests that having an unplanned pregnancy may be an indicator of more unfavorable lifestyle factors among discontinuers.

Of all the maternal and medical factors that we investigated, several were found to be important predictors of THRT discontinuation in early pregnancy. Non-compliance with taking recommended nutritional supplements was the maternal factor that showed the strongest positive association with THRT discontinuation. This finding is somewhat consistent with the findings of Juch *et al.* (8). For example, their study found that non-use of folic acid supplements led to 46-fold increased odds for non-adherence to THRT; in the current study, this increase was smaller i.e. 2.5-fold increased odds.

Our study found that women who were not taking co-medication for mental disorders had a 64% increased odds for discontinuing THRT in early pregnancy. Reluctance to seek medical support (21), missed diagnoses, and an unwillingness to take medications (21) seem to be especially relevant for women with depression during pregnancy. An association with similar magnitude and direction was detected for smoking during pregnancy. Even though the related 95% CI crossed the null effect, this poorer health behavior is plausibly linked to a lack of adequate prenatal care, which may in turn negatively affect treatment with appropriate medications during pregnancy. Nevertheless, this association could also represent a maternal compensatory behavior, i.e. minimizing fetal exposure to medications to compensate for cigarette smoking.

The detected negative association between having a medicated somatic comorbidity and discontinuation of THRT was of medium magnitude (44% reduced risk) and could be explained by closer contact with health professionals for women who were taking other medications for chronic disorders. As a consequence, these women may have received better clinical advice and evidence-based counselling about the risk posed by medication exposures during early pregnancy.

A study on supplement use in Norway (22) revealed that despite recommendations, around 40% of women failed to use folic acid supplements to reduce the risk of neural tube defects. Lack of information about supplement use has been identified as cause of poor uptake in Norwegian women during early pregnancy (22,23). One can speculate that having limited knowledge about THRT could explain its discontinuation.

In contrast to Juch *et al.* (8), we found no association between THRT discontinuation and marital status, age, or pregnancy planning. The differences in findings may be explained in part by the difference in study size and by regional or demographic factors. For instance, whereas marital status may be a defining factor in other European countries and in North America, this is not the case in Norway, where women are more socially and economically independent (24).

Although some of the associations identified in the analysis of multiply imputed datasets were not replicated in the complete case analysis, the similarity in the magnitude of the effect estimates suggests that such discrepancies were likely secondary to decreased study power in the latter analytical set (25). Furthermore, the role of chance cannot be ruled out.

The associative factors illustrate that health-conscious behavior drove the discontinuation of THRT and indirectly confirm our initial hypothesis. Taking action to ensure that the general public is better informed about thyroid disorders, especially during pregnancy, might close existing knowledge gaps and improve drug utilization.

One strength of the study is its large sample size, and its nationwide coverage and prospective design are also strengths (9,11). Notably, we had access to a mandatory nationwide birth registry, the MBRN, which allowed us to investigate an extended range of possible risk factors and to obtain records of chronic disorders (9). Using data from both the MBRN and MoBa allowed us to obtain a more complete picture of a woman's health status during pregnancy and, specifically, of her thyroid disorder. The use of these two data sources represents an important advantage over previous studies. Another strength is that self-reported medication use may more closely reflect actual medication use compared to, for example, prescription records (26). In the MoBa Q1, the women's recall about past and/or concurrent illness was indication-specific, which enhances recollection and limits the risk of misclassification (27). Subgroup and sensitivity analyses validated the robustness of our findings. The use of proper imputation analysis, rather than simply excluding missing data, leads to less biased estimates (18) and can be considered another strength of the study.

A potential limitation of the study is the unavailability of biomarkers to determine the severity of hypothyroidism. However, the prevalence of hypothyroidism in the present study mirrored the prevalence of overt hypothyroidism in the general birthing population, suggesting that this limitation may not be an important concern. The relatively low participation rate of 41%, as well as the participation of healthier women than the general birthing population, may have

led to selection bias (9,11). Smoking and a negative pregnancy history were borderline associated with discontinuation, and women with these characteristics were underrepresented in MoBa; thus, we might have underestimated the true discontinuation rate in this population. Finally, we cannot rule out that there might be other unmeasured factors, such as maternal behavioral traits, psychological correlates or personality traits (8), that may have impacted our results.

In conclusion, this study reported the extent of THRT discontinuation in early pregnancy and determined the predictive risk factors for discontinuation. The study population was large and our results were consistent with earlier findings, supporting the reliability and even the generalizability of our findings. To improve drug utilization during early pregnancy, it may be helpful to integrate information about a woman's overall health with predictive risk factors to estimate the likelihood of THRT discontinuation. Our results should be interpreted with these strengths and limitations in mind.

Conclusions

THRT was discontinued by 13.0% of the pregnant women in this study during early pregnancy. Having a non-medicated mental comorbidity and failure to comply with recommended nutritional supplement use were significant predictive risk factors of THRT discontinuation. The presence of a medicated somatic comorbidity significantly reduced this risk.

It is clinically important to identify women who are likely to discontinue hypothyroid medication in early pregnancy. Indeed, doing so may provide evidence-based information about the risk posed by suboptimal medication of hypothyroidism on maternal-child health and help providers give women the information they need to develop an evidence-based understanding of such risks.

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Legends for supporting information

MoBa questionnaires Q1 and Q2. All questionnaires used in the Norwegian Mother and Child Cohort Study can be found online.

Summary: The MoBa questionnaires help explain how the study population and the variables for the analysis were selected.

Table S1. Comparison of complete and missing information for key variables.

Summary: Table S1 compares the distribution of complete and missing information for key variables. Significant differences ($p<0.05$) indicate that the missing data depend on other covariates rather than occurring completely at random.

Figure and tables legends

Figure 1. Flow chart of the study population.

Table 1. Characteristics of the study population according to thyroid hormone replacement therapy status in early pregnancy (n=1587).

Table 2. Crude OR and multivariate-adjusted OR for discontinuation of thyroid hormone replacement therapy in early pregnancy (n=1587).

Table 1. Characteristics of the study population according to thyroid hormone replacement therapy status in early pregnancy (n=1587).

Variable[a]	Study population n=1587 (%)	Thyroid hormone replacement therapy in early pregnancy		Dis-/vs. Continuers *p*
		Continuers, n=1380 (%)	Discontinuers, n=207 (%)	
Maternal age at delivery (years)				
<25	86 (5.4)	69 (5.0)	17 (8.2)	0.040
25–30	406 (25.6)	353 (25.6)	53 (25.6)	
31–35	663 (41.8)	572 (41.4)	91 (43.9)	
>35	432 (26.6)	386 (27.9)	46 (22.2)	
Marital status				
Married/cohabiting	1522 (95.9)	1325 (96.0)	197 (95.2)	0.630
Single/divorced/separated	65 (4.1)	55 (4.0)	10 (4.8)	
BMI at conception (mean ± SD)	25.6 ± 5.2	25.6 ± 5.2	25.5 ± 5.7	0.822
Missing	45 (2.8)	36 (2.6)	9 (4.3)	
Education, ongoing[b]				
Low	467 (29.4)	385 (27.9)	82 (39.6)	<0.001
Medium	654 (41.2)	576 (41.7)	78 (37.6)	
High	430 (27.1)	391 (28.3)	39 (18.8)	
Missing	36 (2.3)	28 (2.0)	8 (3.8)	
Income[c]				
Low	425 (26.8)	354 (25.6)	71 (34.3)	0.008
Medium	880 (55.4)	779 (56.4)	101 (48.8)	
High	227 (14.3)	198 (14.3)	29 (14.0)	
Missing	55 (3.5)	49 (3.5)	6 (2.9)	
Smoking				
Yes	89 (5.6)	67 (4.8)	22 (10.6)	<0.001
No	1492 (94.0)	1308 (94.8)	184(88.8)	
Missing	6 (0.3)	5 (0.4)	1(0.5)	
Alcohol consumption				
Yes	188 (11.8)	161 (11.7)	27 (13.0)	0.557
No	1384 (87.2)	1207 (87.5)	177 (85.5)	
Missing	15 (0.9)	12 (0.8)	3 (1.4)	
Planned pregnancy				
Yes	1275 (80.3)	1122 (81.3)	153 (73.9)	0.005
No	295 (18.6)	244 (17.7)	51 (24.6)	
Missing	17 (1.1)	14 (1.0)	3 (1.4)	
Parity				
Nulliparous	612 (38.6)	531 (38.5)	81 (39.1)	0.895
Multiparous	975 (61.4)	849 (61.5)	126 (60.8)	
LTHMD				
Yes	135 (8.5)	114 (8.3)	21 (10.1)	0.259
No	1435 (90.4)	1258 (91.2)	177 (85.5)	
Missing	17 (1.1)	8 (0.6)	9 (4.3)	
Symptoms of anxiety/depression (SCL-5 score)[e]				
Yes	43 (2.7)	36 (2.6)	7 (3.4)	0.557
No	1499 (94.4)	1309 (94.9)	190 (91.8)	
Missing	45 (2.8)	35 (2.2)	10 (4.8)	
Reproductive history				

Previous negative event[d]	597 (37.6)	511 (37.0)	86 (41.5)	0.128
No previous negative event	958 (60.4)	843 (61.1)	115 (55.5)	
Missing	32 (2.0)	26 (1.9)	6 (2.9)	
Somatic comorbidity				
No	1201 (75.7)	1039 (75.3)	162 (78.3)	0.017
Medicated	203 (12.8)	187 (13.6)	16 (7.7)	
Non-medicated	183 (11.5)	154 (11.2)	29 (14.0)	
Mental comorbidity				
No	1355 (85.4)	1188 (86.1)	167 (80.7)	0.014
Medicated	82 (5.2)	71 (5.1)	11 (5.3)	
Non-medicated	150 (9.5)	121 (8.8)	29 (14.0)	
Recommended supplement use				
No	672 (42.3)	539 (39.1)	133 (64.3)	<0.001
Yes	915 (57.6)	841 (60.9)	74 (35.7)	
Recommended fiber intake				
Yes	805 (50.7)	692 (50.2)	113 (54.5)	0.189
No	782 (49.3)	688 (49.8)	94 (45.4)	

[a] If not otherwise indicated, the results are presented as n (%).
[b] Education level: low, < 12 years of education; medium, 13–16 years of education; high > 16 years of education (MoBa Q1).
[c] Women's income status (NOK/year): low, < 125000; medium, < 125000–425000; high, > 425000 (MoBa Q1). 1 NOK ≈ 0.12 US dollar.
[d] Previous negative events include spontaneous abortion/stillbirth, ectopic pregnancy, and termination of pregnancy (MoBa Q1).
Total missing data: 14.2%.
Abbreviations: BMI, Body Mass Index**;** LTHMD, life-time history of major depression; NOK, Norwegian kroner; SCL-5 score, short version of the Hopkins Symptom Checklist-25 (SCL-25); SD, standard deviation; *p*, *p*-value; US, United States of America

Table 2. Crude OR and multivariate-adjusted OR for discontinuation of thyroid hormone replacement therapy in early pregnancy (n=1587).

Variable	Crude OR (95% CI)	*p*	Adjusted OR (95%CI)	*p*
Maternal age at delivery (years)				
<25	1.64 (0.90–2.97)	0.103	1.20 (0.64–2.25)	0.550
25–30	1		1	
31–35	1.05 (0.73–1.52)	0.756	1.12 (0.76–1.64)	0.553
>35	0.79 (0.51–1.21)	0.288	0.80 (0.51–1.26)	0.347
Smoking				
Yes	2.31 (1.39–3.84)	0.001	1.64 (0.97–2.79)	0.065
No	1		1	
Income				
Low	1.56 (1.12–2.17)	0.008	1.24 (0.86–1.77)	0.236
Medium	1		1	
High	1.11 (0.70–1.77)	0.643	1.45 (0.88–2.38)	0.137
Education, ongoing				
Low	1.56 (1.11–2.19)	0.009	1.20 (0.83–1.74)	0.327
Medium	1		1	
High	0.74 (0.49–1.13)	0.172	0.75 (0.48–1.15)	0.195
Reproductive history				
Previous negative event	1.22 (0.90–1.66)	0.188	1.31 (0.95–1.81)	0.089
No previous negative event	1		1	
LTHMD				
Yes	1.45 (0.89–2.36)	0.132	1.19 (0.69–2.05)	0.512
No	1		1	
Planned pregnancy				
Yes	0.65 (0.46–0.92)	0.016	0.93 (0.65–1.35)	0.734
No	1		1	
Somatic comorbidity				
No	1		1	
Medicated	0.54 (0.31–0.94)	0.029	0.56 (0.33–0.98)	0.043
Non-medicated	1.20 (0.78–1.85)	0.387	1.12 (0.72–1.74)	0.591
Mental comorbidity				
No	1		1	
Medicated	1.10 (0.57–2.12)	0.772	0.99 (0.49–1.99)	0.993
Non-medicated	1.70 (1.10–2.64)	0.017	1.64 (1.03–2.63)	0.036
Recommended supplement use				
Yes	1		1	
No	2.80 (2.06–3.80)	<0.001	2.51 (1.82–3.47)	<0.001
Recommended fiber intake				
Yes	1	0.241	1	0.112
No	0.84 (0.62–1.13)		0.77 (0.57–1.05)	

Abbreviations: CI, confidence interval; LTHMD, life-time history of major depression; OR, odds ratio; *p*, *p*-value.