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Depression and Anxiety during Pregnancy: The Influence of Maternal Characteristics

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Abstract

Introduction: Depression and anxiety during pregnancy are associated with adverse health outcomes for both mother and child. This study aimed to investigate the occurrence of symptoms of depression and anxiety in early and late pregnancy, the longitudinal changes from early to late pregnancy, and factors associated with symptoms of depression and anxiety in pregnant women in the Netherlands.

Methods: We studied 2897 women participating in the PRegnancy and Infant DEvelopment (PRIDE) Study. To assess symptoms of depression and anxiety, web-based questionnaires including the Hospital Anxiety and Depression Scale (HADS) and multiple questions on maternal characteristics, including demographics, health, and lifestyle factors, were completed in early and late pregnancy. Cross-sectional and longitudinal multivariable linear regression analyses were conducted.

Results: According to the HADS, the prevalence of depression in our population increased from 5.4% in early pregnancy to 10.0% in late pregnancy (p < 0.001), whereas the prevalence of anxiety decreased from 17.9% to 14.2% (p < 0.001). Several maternal characteristics, such as level of education, multiparity, a history of depression, severe nausea, extreme fatigue, lack of physical exercise, and negative life events were associated with symptoms of depression and/or anxiety throughout pregnancy. Being non-Dutch, not living with a partner, and having an unplanned pregnancy or a prolonged time to pregnancy influenced the depression and/or anxiety scores in early pregnancy only.

Conclusions: Depression and anxiety are common disorders in both early and late pregnancy. Screening for risk factors for these disorders in early pregnancy is important, since prenatal depression and anxiety may be related to adverse maternal and child health outcomes.

Keywords

Depression, Anxiety, Pregnancy, Maternal exposure, PRIDE Study, Psychological epidemiology

Introduction

Maternal depression and anxiety during pregnancy are an important research topic, as both have been associated with a broad range of adverse health outcomes for mother and child [1-8]. Several studies found associations between maternal depression and/or anxiety and either lower birth weight or shorter gestational age or both [4,9-12]. Since these outcomes may lead to increased childhood mortality and long-term morbidity, [13,14] they may have an enormous impact on public health and future health care. Furthermore, maternal depression and anxiety may have negative

consequences for, amongst others, social, behavioral, and neurodevelopment of the child [6,15-17]. Furthermore, prenatal depression and anxiety have also been associated with adverse health outcomes for the mother, such as pre-eclampsia, decreased quality of life, and have been linked to an increased risk of postpartum depression [18-26]. Women with high levels of depressive symptoms in late pregnancy may not only show more symptoms of depression directly after birth, but even after 14 years of follow-up [27-28].

Data regarding prevalence rates of depression and anxiety and changes over time during pregnancy vary widely. In general, prevalence rates of anxiety seem to be higher compared to prevalence rates of depression [29-32]. For the latter, some reported a decrease from 11.0% to 8.5% over the course of pregnancy [33], while others reported an increase from 7.4% in early pregnancy to 12.8% in middle, and 12.0% in late pregnancy [34], or a U-shaped form with the lowest rate around 24 weeks of gestation [31]. Prevalence rates of anxiety and changes over time during pregnancy have been studied less extensively compared to depression, with prevalence rates ranging from 15.0% to 36.3% [29,31,32,35]. Some reported an increase in anxiety [36], while others reported a U-shaped pattern [31,37], or a decrease over the course of pregnancy [38]. Differences in prevalence rates could be explained by heterogeneity among studies, for example due to differences in sociodemographic background [34]. Furthermore, depression and anxiety were assessed in different ways, for example, based on questionnaires or structured interviews, or on a diagnosis made by a professional.

As prenatal depression and anxiety seem to be strongly associated with adverse maternal and child-health outcomes, they are an important public health concern. Specific information regarding prevalence rates, longitudinal changes, and risk factors is necessary to provide adequate counseling and therapy during pregnancy to prevent adverse health outcomes for mother and child. Therefore, this exploratory study aimed to investigate the prevalence rates of symptoms of depression and anxiety in early and late pregnancy, as well as changes over time from early to late pregnancy in a large sample of pregnant women. Furthermore, we examined the associations of several maternal characteristics with symptoms of depression and anxiety during pregnancy.

Materials and Methods

General design PRIDE study

This study was embedded in the PRegnancy and Infant DEvelopment (PRIDE) Study, an ongoing prospective cohort study in the Netherlands. The PRIDE Study aims to include a large number of pregnant Dutch women in early pregnancy to answer a broad range of research questions pertaining to maternal and child health and development.

More details concerning the rationale and design of the PRIDE Study are reported elsewhere [39]. In short, pregnant women were invited to participate in the study by their prenatal care provider (i.e. midwife, gynecologist, or general practitioner) at the first prenatal care visit. After providing informed consent, participating women completed three web-based questionnaires during pregnancy (around gestational weeks 10-12, 17, 34), as well as biannually throughout childhood. The questionnaires included questions on general maternal characteristics, chronic and pregnancy-related conditions, medication use, lifestyle, life events, and other exposures during pregnancy. Exclusion criteria are maternal age below 18 years, more than 16 weeks pregnant at intake, and inability to read and understand the Dutch language. The PRIDE Study was approved by the Regional Committee on Research involving Human Subjects Arnhem-Nijmegen. PRIDE Study participants with an estimated date of delivery from February 2012 through December 2015 were included in the present study. If a woman participated more than once in the PRIDE Study, only the first pregnancy was included.

Measurement tool

Hospital Anxiety Depression Scale (HADS): The PRIDE Study questionnaires in early (weeks 10-12) and late (week 34) pregnancy included the Hospital Anxiety Depression Scale (HADS), a 14-item self-completion screening scale to indicate the possible presence of symptoms of depression and anxiety [40]. The questions assess the experience of symptoms in the past week. The questionnaire consists of two subscales, one for symptoms of depression (HADS-D) and one for symptoms of anxiety (HADS-A), with a 4-point rating scale of severity of symptoms (0-3), adding up to a score range of 0-21 for each subscale. The HADS is a commonly used questionnaire to screen for depression and anxiety both in out-patient clinics and in research settings and is validated in different groups of the Dutch population [41]. A cut-off score ≥ 8 was used for both subscales to identify depression and anxiety [40,42].

Maternal characteristics

Several maternal characteristics were included in this study to examine their associations with the HADS scores.

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Table 1: Maternal characteristics studied.

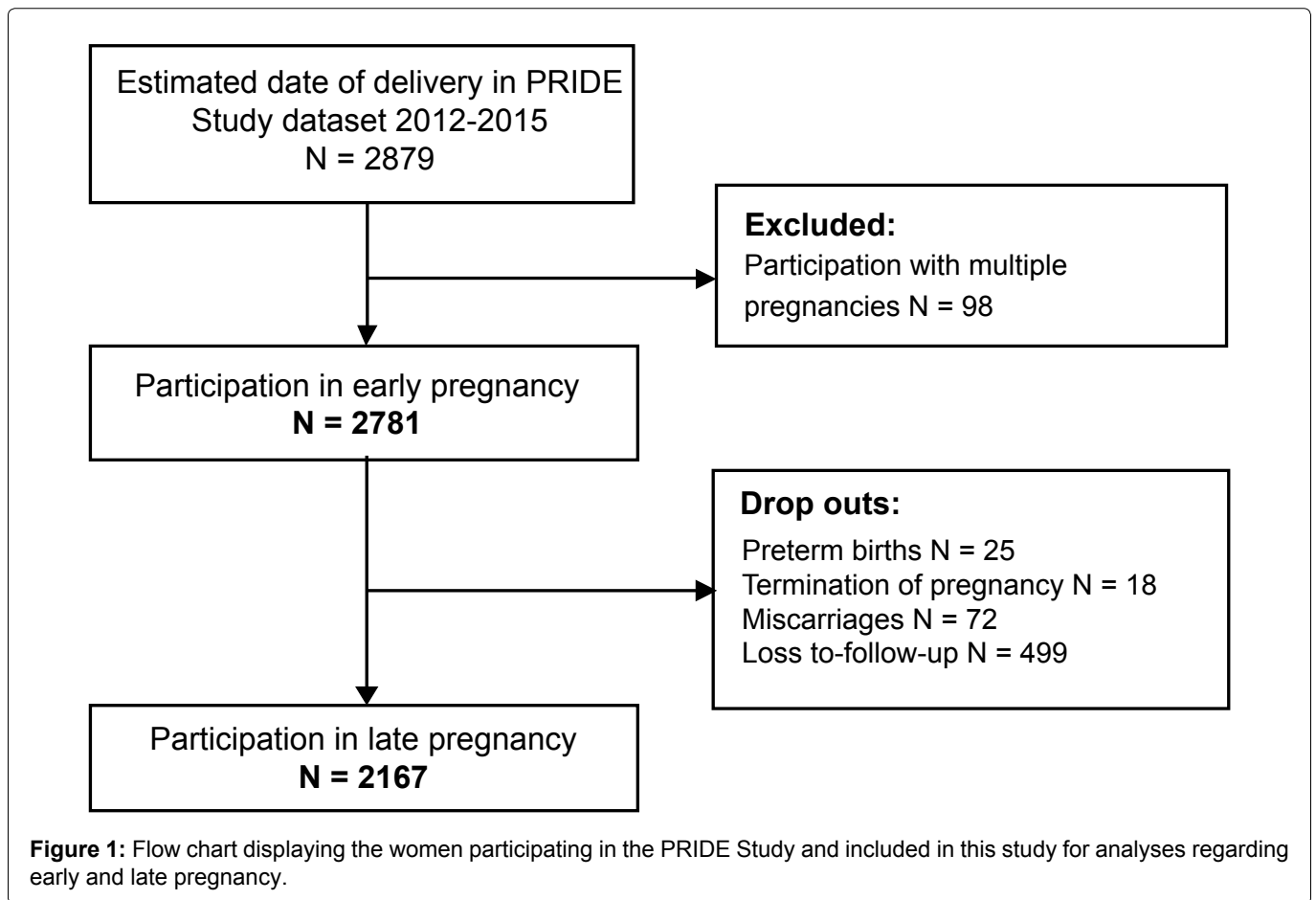|	Maternal characteristics	Categories
Demographics	Maternal age	< 30, 30-34, ≥ 35 years
	Level of education	
		Low
		(no education, lower general secondary education), intermediate (intermediate vocational education, higher general secondary education, pre-university education), high (higher vocational education, university)
	Net household income	< €2500, ≥ €2500 per month
	Population group	Dutch, Non-Dutch
	Living together with partner	Yes, No
Medical history	Parity	0, ≥ 1 previous live births
	Pre-pregnancy Body Mass Index (BMI)	Underweight, normal weight, overweight/obese
	Time to pregnancy	pregnant within first month, 1-12, > 12 months
	Previous miscarriages	Yes, No
	Use of reproductive techniques	Yes, No (Natural Conception)
	Chronic diseases	No presence, presence of any chronic disease (e.g. asthma, hypertension, depression)
Pregnancy-related characteristics	Unplanned pregnancy	Yes, No
	Infections during pregnancy	Yes, No
	Severe nausea ("did you suffer from severe nausea during this pregnancy?")	Yes, No
	Extreme fatigue ("did you suffer from extreme fatigue during this pregnancy?")	Yes, No
	Prenatal diagnostics	Positive, negative outcome
Health behavior during pregnancy	Smoking	Yes, No
	Alcohol consumption	Yes, No
	Caffeine consumption	Normal ≤ 1400 mg, high > 1400 mg
	Physical exercise	No, < 150 minutes/week, ≥ 150 minutes/week
Psychosocial characteristics	Negative life event scale	Total Score 0, ≤ 50, > 50, rated according to the social readjustments rating scale (73)
	Medication use for depression or anxiety disorders in the past 4 months	Yes, No
	History of depression	Yes, No
	First-degree family history of depression	Yes, No

These characteristics were selected based on literature research and discussions among the authors, and were categorized into demographics, medical history, pregnancy-related characteristics, health behavior during pregnancy, and psychosocial characteristics. The specific characteristics within each category are listed in (Table 1). All maternal characteristics were self-reported and obtained from the three prenatal PRIDE Study questionnaires.

Statistical analyses

Based on the HADS-D and HADS-A scores, prevalence rates of depression and anxiety (scores ≥ 8) in our population, as well as mean scores with Standard Deviations (SD) were calculated. Absolute numbers with percentages were used to describe the maternal characteristics, stratified by the presence of depression or anxiety according to the HADS-D and HADS-A, for both early and late pregnancy. To examine changes over time in the HADS-D and HADS-A scores from early to late pregnancy, multivariable linear mixed models with the subjects as random effects with manual backward elimination were applied, using p-values below 0.10 to retain all potentially relevant maternal characteristics in the final models.

Following, we fitted three linear regression models for each of the continuous outcome variables (HADS-D score and HADS-A score): two cross-sectional models, one in early pregnancy and one in late pregnancy, and one longitudinal model. For the cross-sectional models, univariable linear regression analyses were initially conducted for all selected maternal characteristics separately to obtain crude β coefficients (β) with 95% confidence intervals (95% CI). Maternal characteristics that were stable over time, such as education and ethnicity, were included in both models, whereas characteristics measured in early pregnancy were included in the cross-sectional model for early pregnancy only, and characteristics measured in late pregnancy in the model for late pregnancy. Using complete case analyses, adjusted β coefficients were derived from multivariable

Figure 1: Flow chart displaying the women participating in the PRIDE Study and included in this study for analyses regarding early and late pregnancy.

linear regression models initially including all maternal characteristics. Manual stepwise backward elimination was applied to retain only variables with p-values below 0.10 in the models. Thereby, these characteristics were adjusted for all other maternal characteristics in the final models.

For the longitudinal models, multivariable linear regression analyses were done with the HADS-D and HADS-A scores measured in late pregnancy as outcome variables and all maternal characteristics measured in early and late pregnancy as potential determinants. Again, manual stepwise backward elimination was applied to identify all relevant risk factors for symptoms of depression and anxiety in late pregnancy. All statistical analyses were performed using the Statistical Package for Social Sciences, version 22.0 for Windows (IBM Corp., Armonk, NY).

Results

In total, 2897 women were included in this study, of which 2167 women completed the questionnaires in both early and late pregnancy (Figure 1). All results are based on the complete sample of women who filled out the HADS in the specific pregnancy period, except for the results of the longitudinal analyses.

Prevalence rates

Based on the HADS scores, the prevalence of de-pression in our population was 5.4% in early pregnancy (HADS-D mean score: 2.63, SD: 2.50) and 10.0% in late pregnancy (HADS-D mean: 3.66, SD: 2.66). The mixed model analysis showed an increase in HADS-D scores throughout pregnancy (adjusted β 1.50, 95% CI: 1.31-1.68). The prevalence of anxiety was 17.9% in early pregnancy (HADS-A mean: 5.69, SD: 2.19) and 14.2% in late pregnancy (HADS-A mean: 5.35, SD: 2.17), which was consistent with a decrease throughout pregnancy in HADS-A scores in the mixed model (adjusted β -0.21, 95% CI: -0.38- - 0.04).

Cross-sectional analyses of maternal characteristics

The distributions of the maternal characteristics in early and late pregnancy in our population are shown in (Table 2 and Table 3) respectively, stratified by the presence of depression or anxiety according to the HADS, using the predefined cut-off values. The results of the univariable and multivariable linear regression analyses, expressed as crude and adjusted β coefficients with 95% CIs, are shown in (Tables 4 and Table 5). In the univariable analyses, the majority of characteristics seemed to showed associations with the continuous HADS-D and/ or HADS-A scores, but many of these did not contribute independently to the multivariable models. Therefore, only the adjusted β coefficients are described underneath.

Table 2: Maternal characteristics of women with and without depression or anxiety in early pregnancy according to the scores on the HADS-depression (HADS-D) and HADS-anxiety (HADS-A) subscales.

Maternal characteristics[1]	HADS-D - N = 2454 (%)	HADS-D + N = 140 (%)	HADS-A - N = 2118 (%)	HADS-A + N = 463 (%)
Demographics				
Maternal age (years)				
≤ 30	1291 (52.6)	71 (50.7)	1102 (52.0)	256 (55.3)
30-34	903 (36.8)	51 (36.4)	789 (37.3)	161 (34.8)
≥ 35	260 (10.6)	18 (12.9)	227 (10.7)	46 (9.9)
Level of education				
High	1829 (74.5)	91 (65.0)	1583 (74.7)	320 (69.1)
Intermediate	561 (22.9)	40 (28.6)	487 (23.0)	119 (25.7)
Low	54 (2.2)	9 (6.4)	38 (1.8)	24 (5.2)
Net household income (€/month)				
< 2500	322 (13.1)	29 (20.7)	282 (13.3)	69 (14.9)
≥ 2500	1741 (70.9)	81 (57.9)	1505 (71.1)	312 (67.4)
Population group				
Dutch	2374 (96.7)	132 (94.3)	2050 (96.8)	443 (95.7)
Non-Dutch	73 (3.0)	81	60 (2.8)	20 (4.3)
Living together with partner				
Yes	1996 (81.3)	100 (71.4)	1740 (82.2)	350 (75.6)
No	65 (2.6)	10 (7.1)	50 (2.4)	25 (5.4)
Medical history				
Parity				
Primiparity	1410 (57.5)	67 (47.9)	1191 (56.2)	280 (60.5)
Multiparity	1043 (42.5)	73 (52.1)	926 (43.7)	183 (39.5)
Pre-pregnancy BMI				
Normal weight	1670 (68.1)	89 (63.6)	1450 (68.5)	302 (65.2)
Underweight	68 (2.8)	6 (4.3)	57 (2.7)	18 (3.9)
Overweight/obese	539 (22.0)	35 (25.0)	467 (22.0)	102 (22.0)
Time to pregnancy[2]				
< 1 month	649 (28.6)	34 (32.1)	574 (29.3)	115 (27.8)
1-12 months	1324 (58.3)	59 (55.7)	1133 (57.9)	233 (56.4)
> 12 months	284 (12.5)	10 (9.4)	236 (12.1)	63 (15.3)
Previous miscarriages				
Yes	525 (21.4)	28 (20.0)	431 (20.3)	115 (24.8)
No	1929 (78.6)	112 (80.0)	1687 (79.7)	348 (75.2)
Use of reproductive techniques				
Natural conception	2262 (92.2)	134 (95.7)	1969 (93.0)	417 (90.1)
Yes	183 (7.5)	6 (4.3)	142 (6.7)	44 (9.5)
Chronic diseases				
Yes	426 (17.4)	28 (20.1)	360 (17.0)	91 (19.7)
No	2005 (81.7)	109 (77.9)	1739 (82.1)	365 (78.8)
Pregnancy-related characteristics				
Unplanned pregnancy				
Yes	175 (7.1)	34 (24.3)	156 (7.4)	48 (10.4)
No	2272 (92.6)	106 (75.7)	1957 (92.4)	413 (89.2)
Infection during pregnancy				
Yes	1110 (45.2)	67 (47.9)	948 (44.8)	223 (48.2)
No	1195 (48.7)	65 (46.4)	1046 (49.4)	210 (45.4)
Severe nausea				
Yes	486 (19.8)	52 (37.1)	421 (19.9)	111 (24.0)
No	1333 (54.3)	56 (40.0)	1145 (54.1)	237 (51.2)
Extreme fatigue				

Yes	888 (36.2)	77 (55.0)	755 (35.6)	205 (44.3)
No	931 (37.9)	31 (22.1)	815 (38.5)	142 (30.7)
Health behaviour during pregnancy				
Smoking				
Yes	136 (5.5)	17 (12.1)	111 (5.2)	44 (9.5)
No	2316 (94.4)	123 (87.9)	2006 (94.7)	418 (90.3)
Alcohol				
Yes	366 (14.9)	29 (20.7)	314 (14.8)	76 (16.4)
No	2083 (84.9)	110 (78.6)	1801 (85.0)	384 (82.9)
Caffeine consumption				
Normal (≤ 1400 mg)	1814 (73.9)	105 (76.0)	1570 (74.1)	343 (74.1)
High (> 1400 mg)	610 (24.9)	33 (23.6)	521 (24.6)	116 (25.1)
Physical exercise				
No	167 (6.8)	27 (19.3)	144 (6.8)	49 (10.6)
< 150 m/week	1038 (42.3)	54 (38.6)	884 (41.7)	196 (42.3)
≥ 150 min/week	1247 (50.8)	56 (40.0)	1086 (51.3)	217 (46.9)
Psychosocial characteristics				
Negative live event score				
0	1894 (77.2)	95 (67.9)	1647 (77.8)	331 (71.5)
≤ 50	424 (17.3)	32 (22.9)	365 (17.2)	91 (19.7)
> 50	136 (5.5)	13 (9.3)	106 (5.0)	41 (8.9)
Use of medication for depression or anxiety disorders				
Yes	20 (0.8)	6 (4.3)	15 (0.7)	11 (2.4)
No	2268 (92.4)	120 (85.7)	1978 (93.4)	397 (85.7)
History of depression				
Yes	552 (22.5)	50 (35.7)	426 (20.1)	172 (37.1)
No	1893 (77.1)	90 (64.3)	1685 (79.6)	289 (62.4)
Family history of depression				
Yes	610 (24.9)	50 (35.7)	485 (22.9)	167 (36.1)
No	1843 (75.1)	90 (64.3)	1632 (77.1)	296 (63.9)

[1]Numbers of women within the strata do not add up to the total number of women for all variables due to missing values; [2]Women with planned pregnancies only.

Table 3: Maternal characteristics of women with and without depression or anxiety in late pregnancy according to the scores on the HADS-depression (HADS-D) and HADS-anxiety (HADS-A) subscales.

Maternal characteristics[1]	HADS-D - N = 1910 (%)	HADS-D + N = 213 (%)	HADS-A - N = 1781 (%)	HADS-A + N = 295 (%)
Demographics				
Maternal age (years)				
≤ 30	995 (52.1)	103 (48.4)	936 (52.6)	150 (50.8)
30-34	722 (37.8)	80 (37.6)	665 (37.3)	112 (38.0)
≥ 35	193 (10.1)	30 (14.1)	180 (10.1)	33 (11.2)
Level of education				
High	1486 (77.8)	126 (59.2)	1372 (77.0)	204 (69.2)
Intermediate	378 (19.9)	77 (36.2)	373 (20.9)	73 (24.7)
Low	34 (1.8)	6 (2.8)	25 (1.4)	13 (4.4)

Net household income (€/month)				
< 2500	251 (13.1)	47 (22.1)	232 (13.0)	61 (20.7)
≥ 2500	1528 (80.0)	147 (69.0)	1424 (80.0)	212 (71.9)
Population group				
Dutch	1835 (96.1)	203 (95.3)	1709 (96.0)	281 (95.3)
Non-Dutch	65 (3.4)	6 (2.8)	63 (3.5)	9 (3.1)
Living together with partner				
Yes	1720 (90.1)	183 (85.9)	1609 (90.3)	252 (85.4)
No	58 (3.0)	8 (3.8)	45 (2.5)	20 (6.8)
Medical history				
Parity				
Primiparity	1111 (58.2)	90 (42.3)	1023 (57.4)	157 (53.2)
Multiparity	799 (41.8)	123 (57.7)	758 (42.6)	138 (46.8)
Pre-pregnancy BMI				
Normal weight	1318 (69.0)	129 (60.6)	1222 (68.6)	189 (64.1)
Underweight	61 (3.2)	5 (2.3)	52 (2.9)	11 (3.7)
Overweight/obese	401 (21.0)	60 (28.2)	386 (21.7)	70 (23.7)
Time to pregnancy[2]				
< 1 month	494 (27.9)	58 (31.5)	476 (28.8)	66 (25.2)
1-12 months	1041 (58.8)	102 (55.4)	959 (58.1)	156 (59.5)
> 12 months	226 (12.8)	23 (12.5)	207 (12.5)	38 (14.5)
Previous miscarriages				
Yes	403 (21.1)	59 (27.7)	381 (21.4)	64 (21.7)
No	1507 (78.9)	154 (72.3)	1400 (78.6)	231 (78.3)
Use of reproductive techniques				
Natural conception	1757 (92.0)	203 (95.3)	1653 (92.8)	265 (89.9)
Yes	144 (7.5)	10 (4.7)	122 (6.9)	27 (9.2)
Chronic diseases				
Yes	321 (16.8)	43 (20.2)	297 (16.7)	55 (18.6)
No	1570 (82.2)	163 (76.5)	1464 (82.2)	234 (79.3)
Pregnancy-related characteristics				
Unplanned pregnancy				
Yes	131 (6.9)	29 (13.6)	126 (7.1)	30 (10.2)
No	1771 (92.7)	184 (86.4)	1650 (92.6)	262 (88.8)
Infection during pregnancy				
Yes	904 (47.3)	123 (57.7)	844 (47.4)	152 (51.5)
No	911 (47.7)	74 (34.7)	849 (47.7)	121 (41.0)
Severe nausea				
Yes	104 (5.4)	22 (10.3)	94 (5.3)	25 (8.5)
No	1775 (92.9)	186 (87.3)	1657 (93.0)	265 (89.8)
Extreme fatigue				
Yes	136 (7.1)	49 (23.0)	126 (7.1)	53 (18.0)
No	1433 (75.0)	127 (59.6)	1341 (75.3)	203 (68.8)
Prenatal diagnostics				
Negative outcome	200 (10.5)	18 (8.5)	177 (9.9)	35 (11.9)
Positive outcome	1710 (89.5)	195 (91.5)	1604 (90.1)	260 (88.1)
Health behaviour during pregnancy				

Smoking				
Yes	40 (2.1)	15 (7.0)	43 (2.4)	9 (3.1)
No	1852 (97.0)	192 (90.1)	1719 (96.5)	280 (94.9)
Alcohol				
Yes	49 (2.6)	8 (3.8)	42 (2.4)	13 (4.4)
No	1845 (96.6)	199 (93.4)	1721 (96.6)	277 (93.9)
Caffeine consumption				
Normal (≤ 1400 mg)	1355 (70.9)	51 (23.9)	451 (25.3)	204 (69.2)
High (> 1400 mg)	488 (25.5)	148 (69.5)	1266 (71.1)	75 (25.4)
Physical exercise				
No	154 (8.1)	38 (17.8)	155 (8.7)	36 (12.2)
< 150 m/week	910 (47.6)	102 (47.9)	846 (47.5)	149 (50.5)
≥ 150 min/week	841 (44.0)	73 (34.3)	776 (43.6)	110 (37.3)
Psychosocial characteristics				
Negative live event score				
0	1346 (70.5)	131 (61.5)	1260 (70.7)	180 (61.0)
≤ 50	409 (21.4)	58 (27.2)	380 (21.3)	78 (26.4)
> 50	155 (8.1)	24 (11.3)	141 (7.9)	37 (12.5)
Use of medication for depression or anxiety disorders				
Yes	10 (0.5)	1 (0.5)	5 (0.3)	5 (1.7)
No	1864 (97.6)	201 (94.4)	1743 (97.9)	276 (93.6)
History of depression				
Yes	411 (21.5)	74 (34.7)	348 (19.5)	122 (41.4)
No	1491 (78.1)	136 (63.8)	1424 (80.0)	171 (58.0)
Family history of depression				
Yes	476 (24.9)	64 (30.0)	435 (24.4)	93 (31.5)
No	1431 (74.9)	147 (69.0)	1343 (75.4)	200 (67.8)

[1]Numbers of women within the strata do not add up to the total number of women for all variables due to missing values; [2] Women with planned pregnancies only.

Table 4: Cross-sectional models for the associations between maternal characteristics and continuous scores on the HADS-depression (HADS-D) and HADS-anxiety (HADS-A) subscales in early pregnancy.

Maternal characteristics	HADS-D		HADS-A	
	Crude β	Adjusted β	Crude β	Adjusted β
Demographics				
Maternal age (years)				
≤ 30	Ref	-	Ref	Ref
30-34	0.04 (-0.17-0.24)		-0.14 (-0.32-0.04)	-0.07 (-0.33-0.18)
≥ 35	0.16 (-0.16-0.49)		-0.01 (-0.29-0.28)	-0.50 (-0.92- - 0.07)
Level of education				
High	Ref	Ref	Ref	-
Intermediate	0.53 (0.30-0.76)	0.27 (-0.03-0.57)	0.16 (-0.04-0.36)	
Low	1.61 (0.99-2.24)	1.10 (0.32-1.89)	1.43 (0.88-1.98)	
Net household income < €2500/mo (€ / month)	0.73 (0.45-1.01)	-	0.46 (0.21-0.71)	-
Non-Dutch	0.74 (0.19-1.29)	1.11 (0.38-1.83)	0.39 (-0.10-0.88)	-
Not living together with partner	1.25 (0.68-1.82)	1.45 (0.71-2.18)	1.24 (0.75-1.74)	1.12 (0.35-1.89)
Medical history				
Multiparity	0.56 (-0.10-1.23)	-	-0.07 (-1.33- - 0.07)	-

Pre-pregnancy BMI				
Normal weight	Ref	-	Ref	-
Underweight	0.56 (-0.02-1.14)		0.07 (-0.44-0.57)	
Overweight/obese	0.30 (0.06-0.53)		0.16 (-0.05-0.37)	
Time to pregnancy				
< 1 month	Ref	-	Ref	Ref
1 month-12 months	-0.14 (-0.36-0.07)		-0.02 (-0.22-0.18)	0.03 (-0.24-0.30)
> 12 months	-0.14 (-0.47-0.18)		0.35 (0.06-0.65)	0.57 (0.18-0.95)
Previous miscarriages	0.23 (-0.01-0.47)	-	0.33 (0.12-0.53)	-
Use of reproductive techniques	-0.16 (-0.53-0.21)	-	0.31 (-0.02-0.63)	-
Chronic diseases	0.21 (-0.04-0.46)	-	0.33 (0.11-0.54)	-
Pregnancy-related characteristics				
Unplanned pregnancy	1.29 (0.94-1.64)	0.73 (0.21-1.25)[*]	0.55 (0.24-0.87)	-
Infection during pregnancy	0.29 (0.09-0.49)	0.29 (0.04-0.55)	0.22 (0.04-0.39)	-
Severe nausea	1.34 (1.09-1.58)	1.04 (0.75-1.33)	0.25 (0.03-0.47)	-
Extreme fatigue	1.21 (0.99-1.43)	0.74 (0.48-1.00)	0.50 (0.31-0.70)	0.35 (0.11-0.58)
Health behaviour during pregnancy				
Smoking	0.56 (0.15-0.96)	-	0.84 (0.48-1.19)	-
Alcohol	-0.01 (-0.28-0.26)	-	0.13 (-0.10-0.37)	-
High caffeine consumption	-0.37 (-0.59- -0.14)	-	-0.04 (-0.24-0.15)	-
Physical exercise				
≥ 150 min/week	Ref	Ref	Ref	Ref
< 150 m/week	0.28 (0.08-0.48)	0.18 (-0.08-0.44)	0.10 (-0.08-0.27)	0.11 (-0.14-0.35)
No	1.57 (1.20-1.95)	1.33 (0.85-1.82)	0.73 (0.40-1.06)	0.66 (0.20-1.12)
Psychosocial characteristics				
Negative life event score				
0	Ref	Ref	Ref	Ref
≤ 50	0.73 (0.03-1.44)	0.97 (0.22-1.72)	0.82 (0.20-1.44)	0.44 (-0.28-1.16)
> 50	1.37 (0.69-2.04)	0.71 (-0.09-1.50)	2.12 (1.53-2.70)	1.49 (0.72-2.25)
Use of medication for depression or anxiety disorders	2.14 (1.19-3.09)	-	1.42 (0.58-2.26)	-
History of depression	0.77 (0.54-1.00)	0.72 (0.43-1.02)	1.06 (0.86-1.26)	0.92 (0.64-1.21)
Family history of depression	0.48 (0.26-0.70)	-	0.68 (0.48-0.87)	0.59 (0.32-0.86)

-Variable eliminated from the multivariable model; [*]Not adjusted for time to pregnancy and use of reproductive techniques.

Table 5: Cross-sectional models for the associations between maternal characteristics and continuous scores on the HADS-depression (HADS-D) and HADS-anxiety (HADS-A) subscales in late pregnancy.

Maternal characteristics	HADS-D		HADS-A	
	Crude β	**Adjusted β**	**Crude β**	**Adjusted β**
Demographics				
Maternal age (years)				
≤ 30	Ref	-	Ref	-
30-34	0.15 (-0.09-0.39)		0.07 (-0.13-0.27)	
≥ 35	0.48 (0.10-0.86)		0.14 (-0.17-0.46)	
Level of education				
High	Ref	Ref	Ref	Ref
Intermediate	0.86 (0.59-1.13)	0.77 (0.43-1.11)	0.27 (0.05-0.50)	0.31 (0.03-0.59)
Low	1.23 (0.41-2.05)	0.78 (-0.18-1.73)	1.19 (0.50-1.88)	1.37 (0.54-2.20)
Net household income < €2500/mo/mo(€/month)	0.82 (0.50-1.14)	-	0.58 (0.31-0.85)	-
Non-Dutch	0.34 (-0.28-0.97)	-	0.12 (-0.38-0.63)	-
Not living together with partner	0.55 (-0.09-1.20)	-	0.89 (0.36-1.43)	-
Medical history				
Multiparity	0.94 (0.72-1.17)	0.98 (0.69-1.26)	0.15 (-0.04-0.34)	0.22 (-0.02-0.46)
Pre-pregnancy BMI				
Normal weight	Ref	Ref	Ref	-

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Underweight	0.35 (-0.30-1.00)	0.28 (-0.50-1.06)	0.24 (-0.30-0.78)	
Overweight/obese	0.56 (0.28-0.83)	0.37 (0.03-0.71)	0.12 (-0.11-0.34)	
Time to pregnancy				
< 1 month	Ref	-	Ref	-
1 month-12 months	-0.20 (-0.47-0.06)		0.01 (-0.22-0.22)	
> 12 months	-0.17 (-0.56-0.22)		0.08 (-0.24-0.41)	
Previous miscarriages	0.38 (0.10-0.65)	-	0.04 (-0.18-0.27)	-
Use of reproductive techniques	-0.16 (-0.43-0.42)	-	0.10 (-0.27-0.46)	-
Chronic diseases	0.17 (-0.13-0.46)	-	0.07 (-0.18-0.31)	-
Pregnancy-related characteristics				
Unplanned pregnancy	1.09 (0.66-1.51)	-	0.30 (-0.05-0.66)	-
Infection during pregnancy	0.41 (0.18-0.64)	-	0.33 (0.14-0.52)	0.22 (-0.02-0.46)
Severe nausea	0.98 (0.50-1.45)	-	0.68 (0.28-1.08)	-
Extreme fatigue	2.04 (1.64-2.44)	1.58 (1.10-2.07)	1.03 (0.69-1.37)	0.65 (0.22-1.07)
Negative prenatal diagnostics	-0.06 (-0.43-0.31)	-	-0.06 (-0.37-0.25)	-
Health behaviour during pregnancy				
Smoking	1.43 (0.72-2.14)	-	0.53 (-0.06-1.13)	-
Alcohol	0.10 (-0.60-0.79)	-	0.62 (0.04-1.19)	-
High caffeine consumption	-0.25 (-0.51-0.01)	-	0.09 (-0.13-0.30)	-
Physical exercise				
≥ 150 min/week	Ref	Ref	Ref	Ref
< 150 m/week	0.32 (0.09-0.56)	0.21 (-0.09-0.51)	0.13 (-0.07-0.33)	0.27 (0.02-0.52)
No	1.50 (1.09-1.91)	1.60 (1.08-2.11)	0.44 (0.11-0.78)	0.49 (0.06-0.92)
Psychosocial characteristics				
Negative life event score				
0	Ref	Ref	Ref	Ref
≤ 50	0.33 (-0.27-0.93)	0.76 (0.13-1.40)	1.16 (0.68-1.64)	1.38 (0.86-1.91)
> 50	0.76 (0.06-1.47)	0.72 (-0.07-1.51)	1.94 (1.37-2.51)	1.78 (1.11-2.45)
Use of medication for depression or anxiety disorders	1.01 (-0.55-2.57)	-	1.98 (0.65-3.31)	-
History of depression	0.87 (0.60-1.13)	0.60 (0.26-0.93)	1.16 (0.94-1.38)	1.08 (0.80-1.37)
Family history of depression	0.44 (0.18-0.70)	-	0.39 (0.17-0.60)	-

-Variable eliminated from the multivariable model.

Demographics

In early pregnancy only, women of 35 years of age or above had lower scores on the HADS-A subscale compared to women aged < 30 years (β -0.50, 95% CI: -0.92 - - 0.07). Intermediate and low levels of education seemed to increase the HADS-D scores in both early and late pregnancy (low vs. high education: β 1.10, 95% CI: 0.32-1.89 and β 0.78, 95% CI: -0.18-1.73, respectively) and the HADS-A scores in late pregnancy only (low vs high education: β 1.37, 95% CI: 0.54-2.20). No associations were seen for net household income, but women from non-Dutch population groups reported higher scores on the HADS-D in early pregnancy compared to women from Dutch ancestry (β 1.11, 95% CI: 0.38-1.83). Women who did not live together with a partner had increased scores on both the HADS-D and the HADS-A in early pregnancy (β 1.45, 95% CI: 0.71-2.18 and β 1.12, 95% CI 0.35-1.89).

Medical history

Multiparity was related to higher scores on the HADS-D and the HADS-A compared to nulliparity in late pregnancy (β 0.98, 95% CI: 0.69-1.26 and β 0.22, 95% CI: -0.02-0.46). Women who were overweight or obese before pregnancy reported slightly higher scores on the HADS-D in late pregnancy compared to women with normal weight, whereas subfertile women (time to pregnancy > 12 months) reported higher scores on the HADS-A in early pregnancy (β 0.57, 95% CI: 0.18-0.95), but not in late pregnancy. No associations were found for previous miscarriages, the use of reproductive techniques, and the presence of chronic diseases.

Pregnancy-related characteristics

Women with an unplanned pregnancy reported higher scores on the HADS-D in early, but not late pregnancy (β 0.73, 95% CI: 0.21-1.25). Women who had an infection sometime during pregnancy reported slightly higher scores on the HADS-D in early pregnancy and on the HADS-A in late pregnancy than women without infections. Women with severe nausea had higher HADS-D scores in early pregnancy (β 1.04, 95% CI: 0.75-1.33). Extreme fatigue seemed to affect the scores on the HADS-D and the HADS-A throughout pregnancy, with the largest
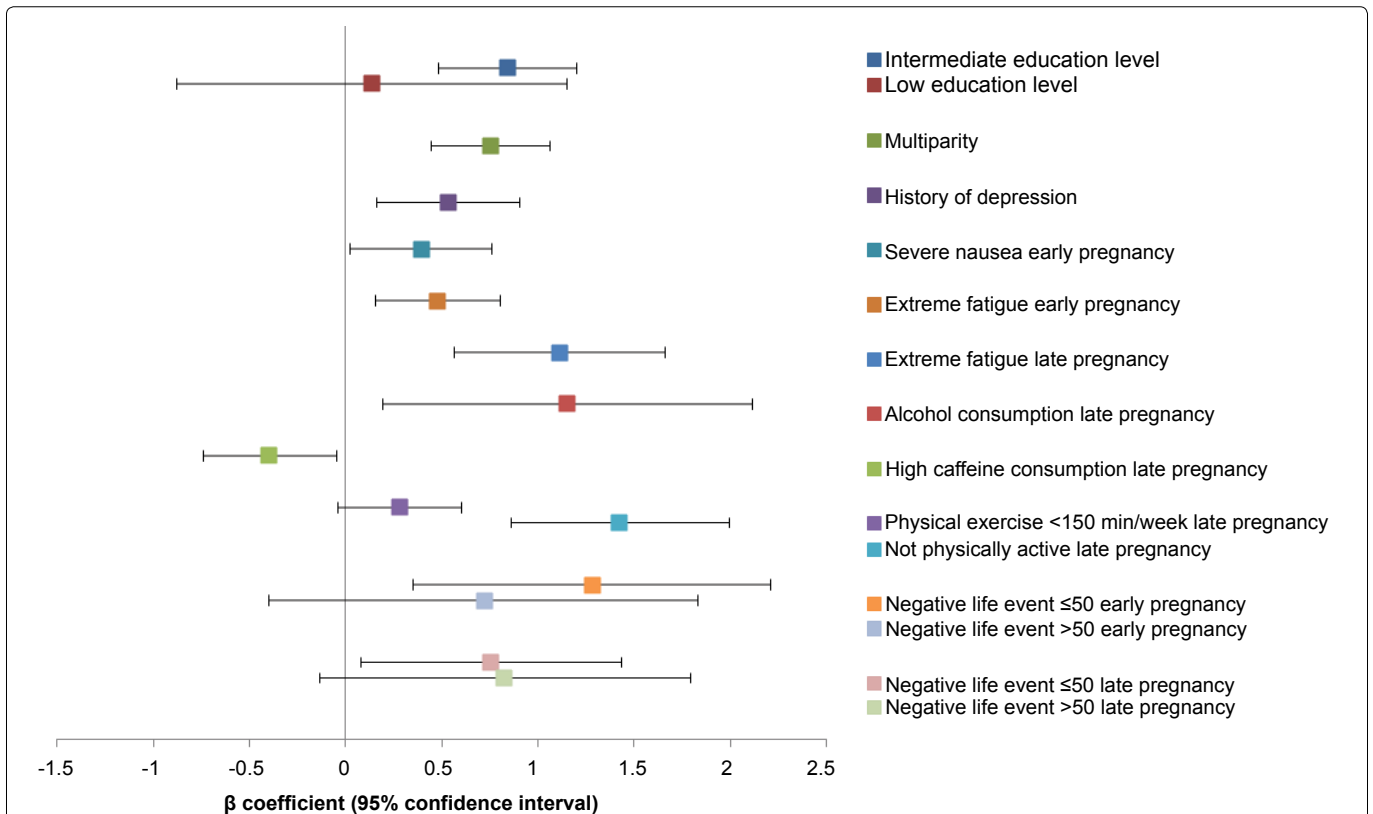
Figure 2: Longitudinal model for the association between maternal characteristics measured in early and late pregnancy and the continuous scores on the HADS-depression (HADS-D) subscale in late pregnancy.

score differences in late pregnancy (β 1.58, 95% CI: 1.10-2.07 and β 0.65, 95% CI: 0.22-1.07). No independent association was found for a negative outcome of prenatal diagnostics.

Health behavior during pregnancy

No influences on the HADS scores were found for smoking, alcohol consumption, and high caffeine consumption in our population. However, not doing any physical exercise compared to exercising 150 minutes or more per week was associated with higher scores on both HADS subscales in early and late pregnancy, but especially with the HADS-D (β 1.33, 95% CI: 0.85-1.82 and β 1.60, 95% CI: 1.08-2.11).

Psychosocial characteristics

Women who experienced negative life events reported higher scores on the HADS-D and HADS-A throughout pregnancy compared to women who did not experience any negative life event. The scores on the HADS-D were around 1.4 and 0.7 points higher for any negative life event in early and late pregnancy, respectively (negative life event score > 0: β 1.35, 95% CI: 0.68-2.01 and β 0.74, 95% CI: 0.04-1.45), while the scores on the HADS-A were on average 1.5 and 1.8 points higher for major negative life events (score > 50) in early and late pregnancy, respectively (β 1.49, 95% CI: 0.72-2.25 and β 1.78, 95% CI: 1.11-2.45). Although med-

ication use for depression or anxiety disorders seemed to be associated with the HADS scores in the univariable analyses, no independent associations were found after adjustment for the other characteristics. However, women with a history of depression reported higher scores on both the HADS-D and the HADS-A in early (β 0.72, 95% CI: 0.43-1.02 and β 0.92, 95% CI: 0.64-1.21) and late pregnancy (β 0.60, 95% CI: 0.26-0.93 and β 1.08, 95% CI: 0.80-1.37). A family history of depression only influenced the scores on the HADS-A in early pregnancy (β 0.59, 95% CI: 0.32-0.86).

Longitudinal analyses

When the characteristics of early and late pregnancy were combined in a longitudinal multivariable model, some characteristics measured in early pregnancy seemed to influenced the HADS scores in late pregnancy. As illustrated in (Figure 2), the following fixed and early pregnancy characteristics were risk factors for symptoms of depression in late pregnancy: intermediate versus high level of education (adjusted β 0.84, 95% CI: 0.48-1.20) but not low level of education, multiparity (adjusted β 0.75, 95% CI: 0.44-1.06), history of depression (adjusted β 0.53, 95% CI: 0.16-0.90), severe nausea (adjusted β 0.39, 95% CI: 0.02-0.76), extreme fatigue (adjusted β 0.47, 95% CI: 0.15-0.80), and negative life events (adjusted β 1.28, 95% CI: 0.35-2.21 for score ≤ 50 and β 0.72, 95% CI: -0.40-1.83 for score > 50). In addition, the already observed associations with extreme fatigue,

Figure 3: Longitudinal model for the associations between maternal characteristics measured in early and late pregnancy and the continuous scores on the HADS-anxiety (HADS-A) subscale in late pregnancy.
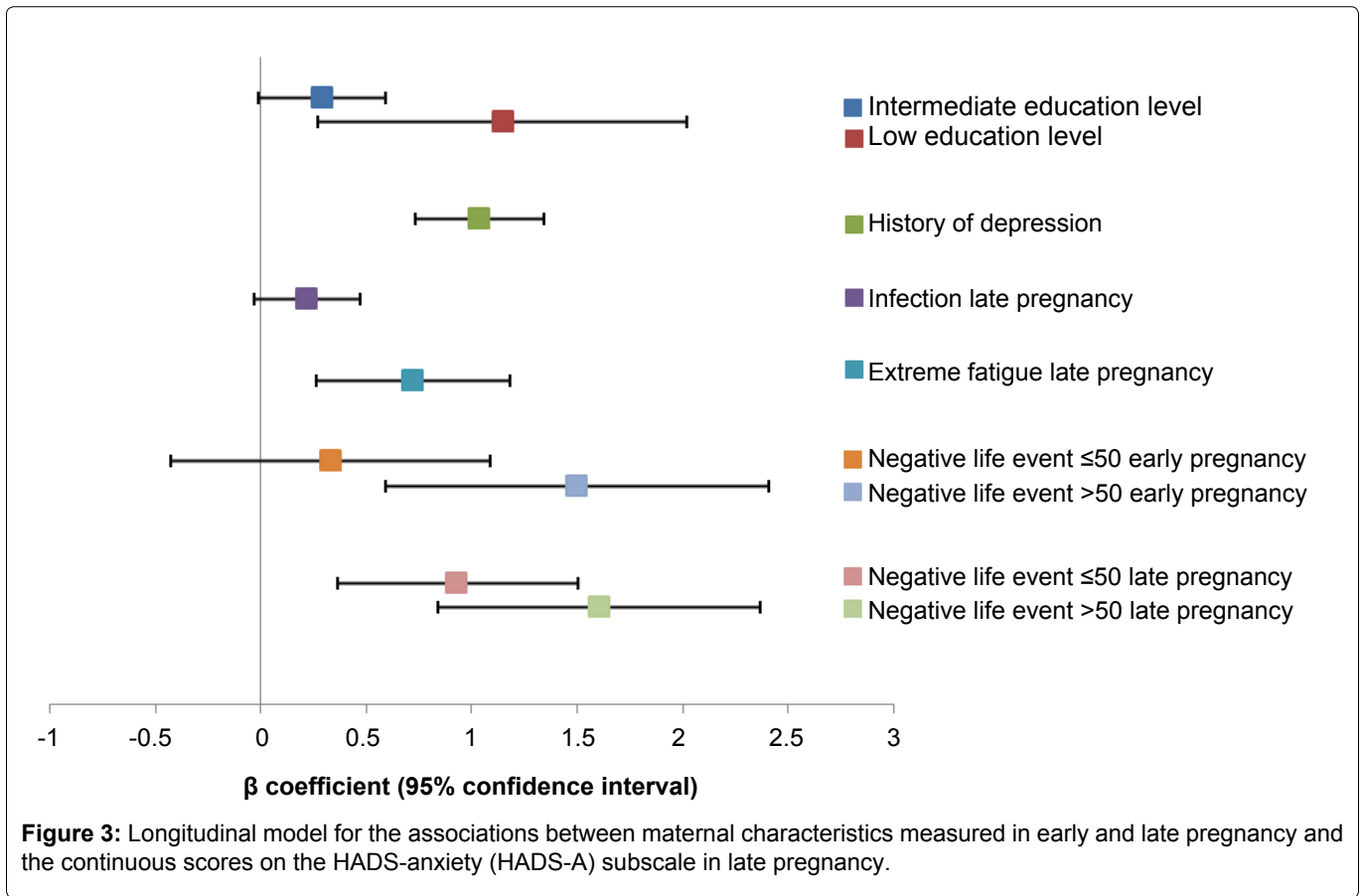
lack of exercise, and negative life events in late pregnancy remained in the longitudinal model, that also showed an adverse effect of alcohol consumption in late pregnancy (β 1.15, 95% CI: 0.19-2.11) and a positive role for high caffeine consumption (β -0.40, 95% CI: -0.74-0.05).

Risk factors for experiencing more symptoms of anxiety in late pregnancy were low or intermediate levels of education (adjusted β 1.15, 95% CI: 0.27-2.02 and β 0.29, 95% CI -0.01-0.59), history of depression (adjusted β 1.04, 95% CI: 0.73-1.34), and major negative life events in early pregnancy (adjusted β 1.50, 95% CI: 0.59-2.41), in addition to the already observed effects of infection, extreme fatigue, and negative life events in late pregnancy. No associations with a lack of exercise were found in the longitudinal model for the HADS-A. These results can be found in (Figure 3).

Discussion

This exploratory study revealed an increase in depression and a decrease in anxiety over the course of pregnancy assessed by the HADS in a large group of 2167 pregnant women from the general population in the Netherlands. The main maternal characteristics associated with depressive symptoms in early and/or late pregnancy were level of education, multiparity, having a history of depression, severe nausea, extreme fatigue, lack of physical exercise, negative life events, and alcohol consumption in late preg-

nancy. Regarding anxiety, associations were mainly found with level of education, having a history of depression, extreme fatigue, lack of exercise, and having experienced negative life events. Being non-Dutch, not living with a partner, having an unplanned pregnancy, and having a long time to pregnancy influenced the depression and/or anxiety scores in early pregnancy only. This study investigated specific information regarding longitudinal changes in depression and anxiety during pregnancy, in combination with a large range of maternal factors that may be associated with symptoms of depression and anxiety.

A strong feature of this study is that the HADS was developed for physically ill patients and therefore filters out somatic symptoms of depression such as fatigue, insomnia, headaches, anergia, and loss of appetite [42,43]. This makes the HADS suitable for use during pregnancy regardless of the physical changes [31]. The HADS is a self-completed screening tool for depression and anxiety, however, and not a diagnostic instrument. By investigating the number of symptoms experienced, slight changes in mood can be detected, which provide more detailed results compared to solely investigating clinical diagnoses of depression and anxiety. Other strengths of this study are its prospective design, the large sample size, availability of information on many maternal characteristics throughout pregnancy, and measurements of symptoms of depression and anxiety at multiple time points during pregnancy using the same

questionnaires. A limitation may be that the study sample consisted of relatively highly educated women, mainly from the Dutch population, which may hamper the generalizability of the results. However, this does not necessarily invalidate the associations found between the HADS scores and maternal characteristics [44,45]. Another limitation may be the self-reported nature of the data, but several validation studies comparing our data to a variety of medical records showed that the validity of most questionnaire items is good to excellent [46-48]. The drop-outs from our cohort had higher prevalence rates of depression and anxiety in early pregnancy compared to women who completed both questionnaires. This is a common problem and combined with the relatively high non-response rate among low educated women suggests that the prevalence rates of symptoms of depression and anxiety in Dutch pregnant women are most likely even higher than measured in this study [36,49,50].

According to the HADS, the prevalence of depression in our population was 5.4% in early and 10.0% in late pregnancy, while the prevalence of anxiety was 17.9% and 14.2% in early and late pregnancy, respectively. Compared to other studies using the same questionnaire, the prevalence rates were lower compared to a Polish population (depression: 15.3%, 12.7%, and 14.0% and anxiety: 27.4%, 23.9%, and 29.9% in early, middle, and late pregnancy, respectively) [37], but higher compared to a Norwegian population (depression: 2.8%, 0.9%, and 4.9%, anxiety: 11.6%, 7.5%, and 12.3%) [51]. Another Dutch population study reported prevalence rates of depression and anxiety of 8.0% and 9.3% in mid-pregnancy, but these were assessed with the Brief Symptom Inventory (BSI) [52].

Previous results regarding the course of depression and anxiety throughout pregnancy were variable [31,33,34,36-38,53], and different types of depression and anxiety disorders may have different patterns pre- and perinatally [54]. In addition, the prevalence rates of depression are not likely to be influenced by differences between countries or regions, but rather by sociodemographic variables [34]. When investigating depression and anxiety, however, it is important to make a distinction between perceived symptoms and clinical diagnoses. A study by Halbreich suggested that the prevalence of mental disorders is not higher during pregnancy, only the prevalence of perceived symptoms [55]. Therefore, the increase in depressive symptoms over time found in our study may partly be explained by higher demands in late pregnancy compared to early pregnancy [34]. Regarding anxiety, we observed a decrease in general symptoms of anxiety over pregnancy. This may be due to different types of anxiety having different patterns over time. Pregnancy-specific anxiety, for example, is seen as a distinct anxiety response in pregnant women [30,56], but other types of anxiety may play a role as well. For future research, we suggest to focus on the presentation of

depression and anxiety, as well as on the biological basis for depression and anxiety in both pregnant and non-pregnant women.

Several maternal characteristics were associated with depression or anxiety in early and/or late pregnancy, and with the increase or decrease in depression and anxiety, respectively. As they were partly associated with different factors, however, depression and anxiety may have a different pathogenesis [31]. In our study, multiparity was a risk factor for depression and anxiety, while results from previous studies are inconsistent [57]. One study reported no effect of parity on depression or anxiety, but found that multiparous women reported higher interpersonal risk factors for anxiety and depression i.e. lower levels of social support and marital satisfaction, with less maladaptive attitudes toward motherhood [58]. Therefore, possible moderating factors should be included in further investigations of the influence of multiparity on depression and anxiety. Severe nausea in early pregnancy was also associated with depression only, whereas previous literature showed that severe nausea with vomiting (hyperemesis gravidarum) was related to both depression and anxiety during pregnancy [59-64].

In line with previous research [65], extreme fatigue was associated with depression, but in our study with anxiety as well. Fatigue is a common symptom of pregnancy and seems less likely to be a sign of depression in pregnant women compared to non-pregnant women [66]. Therefore, extreme fatigue during pregnancy may be considered as a risk factor for depression and anxiety, rather than as a symptom of depression. In the general population, physical exercise may have a positive effect on symptoms of depression and anxiety [67]. Less is known about this topic during pregnancy, although being physically active has been related to fewer symptoms of depression pre- and postnatally [68-70], and regular physical activity was reported to improve anxiety and depression during pregnancy [71]. In our cross-sectional analyses, a lack of physical activity was associated with symptoms of depression and anxiety in both early and late pregnancy, and with depression only in the longitudinal model. It is as yet unclear whether these associations point towards low physical activity as a cause or a consequence of depression and/or fatigue during pregnancy. Having a history of depression was a risk factor for both depression and anxiety in our study, which is in line with previous studies [32,57,58]. Negative life events, which were rated into a robust measure of perceived stress, were also associated with higher prevalence rates of depression and anxiety. Life events are likely to be a source of stress and seem to be associated with depression and anxiety during pregnancy [57,72]. However, the impact of life events on depression and anxiety is not straightforward. First of all, social support and coping strategies play-among others-a

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moderating role on the impact of stress [6,70]. Secondly, the impact of chronic (repeated stressful minor events and daily hassles) versus acute stress should be differentiated, as chronic stress seems to have a more detrimental impact on fetal development compared to acute stress [6]. Finally, the timing of exposure to the stressor is important. Some studies reported that events occurring before 32 weeks were perceived as more stressful than events occurring later in pregnancy [73]. The first half of pregnancy may be a more vulnerable period, as critical life events were linked to increased cortisol levels in early pregnancy only [74]. However, the impact of a major life event on pregnancy outcome (e.g. shortened gestational age) may be greatest during the 5th or 6th month of pregnancy [75]. To determine the influence of life events on depression and anxiety, more research is needed in the above mentioned areas.

In conclusion, the prevalence rates of depression were higher in late pregnancy compared to early pregnancy in our study population. The prevalence rates of anxiety were relatively high, but decreased somewhat from early to late pregnancy. This study identified several risk factors for symptoms of depression and/or anxiety in early and late pregnancy, as well as some factors in early pregnancy that were still associated with depression and anxiety in late pregnancy. Screening for these risk factors in early pregnancy is important to provide adequate support to women at risk at an early stage. As a result, proper counseling and therapy during pregnancy may lead to prevention of adverse maternal and child health outcomes.

Acknowledgements

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