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Research report

Mental disorders in motherhood according to prepregnancy BMI and pregnancy-related weight changes—A Danish cohort study

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ABSTRACT

Background: Previous studies have shown an association between prepregnancy BMI and postpartum depression, but little is known about this association beyond one year postpartum and the influence of postpartum weight retention (PPWR).

Methods: We used data from 70 355 mothers from the Danish National Birth Cohort to estimate the associations between maternal prepregnancy BMI and PPWR, respectively, and incident depression/anxiety disorders until six years postpartum. Outcome was depression or anxiety diagnosed clinically or filling a prescription for an antidepressant. Cox regression was used to estimate hazard ratios (HR) with 95% confidence intervals (CI). Follow-up started at the day of delivery. For the analysis regarding PPWR, follow-up started six months postpartum.

Results: Underweight, overweight and obesity were associated with depression and/or anxiety disorders when compared to normal-weight, though the associations were attenuated after adjustments (HR 1.24 [95% CI 1.06–1.45], 1.05 [95% CI 0.96–1.15] and 1.07 [95% CI 0.95–1.21] for underweight, overweight and obese, respectively).

Compared to mothers who had returned to their prepregnancy BMI, risk of depression/anxiety disorders was increased for mothers, who from prepregnancy to 6 months postpartum experienced either weight loss > 1 BMI unit (HR 1.19 [95% CI 1.06–1.25]), weight gain of 2–3 BMI units (HR 1.23 [95% CI 1.08–1.40]), or weight gain of ≥ 3 BMI units (HR 1.21 [95% CI 1.05–1.40]).

Limitation: Causal direction and mechanisms behind the associations are largely unknown.

Conclusions: Low prepregnancy body weight and postpartum weight gain or loss are associated with occurrence of depression and anxiety disorders.

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1. Introduction

Early motherhood is a psychological challenge for most women (Woolhouse et al., 2014), and pregnancy and the first months after delivery are generally considered periods of high risk for depression (Thombs et al., 2014). Depression has been labelled a leading cause of disability among women (Kessler, 2003; Kontinen et al., 2013; Thombs et al., 2014). The prevalence of postpartum depressions in high income countries, based on clinical interviews or depression screening instruments, has been estimated to up to 19.2% within the

first three months after delivery and the cumulative incidence as high as 14.5% in the same period (Gavin et al., 2005).

Overweight and obesity may increase the risk of both depression and anxiety disorders in the general population (De Wit et al., 2010; Garipey et al., 2010; Luppino et al., 2010) and this association has repeatedly been reported to be stronger for women than men (Atlantis et al., 2005; De Wit et al., 2010; Herva et al., 2006; Kontinen et al., 2013; McCrea et al., 2012; Scott et al., 2005). The possible link between overweight, obesity and poor mental health may be activated by both biological, social, and psychological mechanisms such as inflammation and metabolic changes as well as poor self-esteem (Luppino et al., 2010). High BMI prior to pregnancy as well as postpartum weight retention (PPWR) have also been associated with an increased risk of postpartum depression (Carter et al., 2000; Herring et al., 2008; LaCoursiere et al.,

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2010, 2006; Molyneux et al., 2014) but these studies covered only the first few years after delivery.

Many mothers experience PPWR and studies have found that one in five have a weight retention of 5+ kg 6 to 12 months after delivery (Ohlin and Rossner, 1990; Pedersen et al., 2011). PPWR, which is closely associated with excessive gestational weight gain (Ashley-Martin and Woolcott, 2014; Linne et al., 2004; Mannan et al., 2013), is a risk indicator for later overweight and obesity (Nehring et al., 2011). Thus, if obese mothers are at higher risk of mental disorders, PPWR may have a similar or even higher effect.

Maternal mental health problems have impact on family life, and should be prevented if possible. In this study, we used a cohort of mothers with no prior recorded mental disorders to (1) estimate the association between maternal prepregnancy BMI and incident depression or anxiety disorders in the first 6 years after childbirth, and to (2) estimate how PPWR relates to incident depression or anxiety disorders from 6 months after childbirth up till 6 years postpartum. We hypothesized that high maternal prepregnancy BMI and PPWR independently of initial BMI were associated with a higher risk of depression and/or anxiety in motherhood.

2. Study population and methods

This study was conducted within the Danish National Birth Cohort (DNBC) (Olsen et al., 2001).

From 1996 to 2002, 92 927 pregnant women were recruited to this cohort and information on life style and health during and after pregnancy was collected (Olsen et al., 2001). Briefly, the participating women were invited at their first antenatal visit by their general practitioners to complete four telephone interviews, which were carried out in approximately week 16 and 30 of gestation and 6 and 18 months after delivery. The participation rate was about 60% among invited women.

Data from the interviews were linked with data from the National Patient Register (NPR), the Danish Psychiatric Central Research Register, the Danish National Prescription Registry, and the Danish Civil Registration System (Kildemoes et al., 2011; Lyngge et al., 2011; Mors et al., 2011; Pedersen, 2011; Schmidt et al., 2014) by use of the personal identification number, a unique identifier assigned to all Danish individuals (Pedersen, 2011; Schmidt et al., 2014). All linkage was performed within Statistics Denmark, a governmental institution that collects and maintains electronic records for a broad spectrum of statistical purposes (Thygesen et al., 2011).

The NPR (Lyngge et al., 2011) contains all hospital contacts—both hospitalisations (from 1977) and outpatient visits (from 1995). The Danish Psychiatric Central Research Register contains data on all admissions to the Danish psychiatric inpatient facilities from 1969 (Mors et al., 2011). The diagnostic codes used in these registers are classified according to the Danish versions of the International Classification of Diseases ICD8 from 1977 to 1993 and ICD10 since 1994.

The Danish National Prescription Registry (Kildemoes et al., 2011) includes data on all redeemed prescription drugs in Denmark since 1995. Drugs are categorised according to the Anatomic Therapeutic Chemical (ATC) code, a hierarchical classification system developed by the World Health Organisation (WHO, 2014). The registry holds data on the date of dispensing, the substance, brand name and quantity. The indication for the prescription is not recorded.

From the Danish Civil Registration System (Pedersen, 2011), we retrieved information on deaths and migration to and from Denmark.

We included women from the DNBC who had live born singletons. If a mother was represented with more than one pregnancy in the cohort, we used data only from her first pregnancy. We excluded mothers with no recorded information on prepregnancy weight and

height ($n=1448$). We further excluded mothers with any recorded history of mental illness prior to the day of childbirth ($n=9409$). Any history of mental illness was defined as use of any antidepressants including tricyclic antidepressant (TCA) or any diagnoses of mental disorders leading to an in- or outpatient hospital contact (see Appendix A). Mothers without residence in Denmark at the time of start of follow-up were also excluded ($n=28$). The final study population consisted of 70 355 women.

2.1. BMI and postpartum weight retention

We used prepregnancy BMI calculated from self-reported information on height and weight obtained at the first antenatal interview at gestational week 17 (inter quartile range (IQR) 14–20). BMI was categorised as (a) underweight (< 18.5), (b) normal-weight ($18.5- < 25$), (c) overweight ($25- < 30$), and (d) obese (≥ 30) (WHO, 2000). BMI at 6 months postpartum was calculated based on self-reported information on weight 6 months after birth obtained from the third interview (mean 186 days postpartum (IQR 179–199 days)). Postpartum weight retention was calculated as BMI at 6 months postpartum minus prepregnancy BMI and categorised as (a) weight loss > 1 BMI unit, (b) weight change of $-1- < 1$ BMI unit (reference group), (c) weight gain of $1- < 2$ BMI units, (d) weight gain of $2- < 3$ BMI units, and (e) weight gain of ≥ 3 BMI units. One BMI unit is equivalent to approximately 3 kg for a 1.7 m tall woman.

2.2. Outcome definition

The main outcome was incident cases of depressive disorders or anxiety disorders as defined by medical treatment or clinical diagnosing. Medication of antidepressants is usually prescribed by the woman's general practitioner or less often a private practicing psychiatrist (Mors et al., 2011). We accessed information on all redeemed prescriptions and identified incident cases of depression or anxiety as women who redeemed prescriptions of selective serotonin reuptake inhibitors (SSRIs) (N06AB) or other antidepressants (N06AX) in the Danish National Prescription Registry after the day of delivery. Severe cases of depression and anxiety were defined by the presence of an ICD10 code within F30–39 “All affective mental disorders” or F40–48 “All nervous and stress-related disorders/disorders with physical symptoms” in the NPR or in the Danish Psychiatric Research Register after the day of delivery. These diagnoses were used as a composite endpoint as a marker for psychiatric illness.

Further, we included the calendar year of the beginning of follow-up (categorical) and divided follow-up in early (first 180 days postpartum) or late (181 days to 6 years) cases.

2.3. Statistical analyses

The risk of depression or anxiety associated with each category of prepregnancy BMI was estimated as hazard ratios (HR) with 95% confidence intervals using Cox regression. Follow-up started at the day of delivery and ended at first study outcome, date of a new pregnancy leading to delivery, emigration, death, 6 years after the initial delivery or end of study period (October 10th 2007), whatever came first.

October 10th 2007 was used as the end of study period, since data from the Danish Psychiatric Research Register was only available until October 10th 2007. However, since the follow-up period was restricted to 6 years, this only reduced follow-up for 6121 mothers (8.7% of the total number of eligible mothers).

Analyses were performed for the overall period (from delivery to 6 years postpartum) as well as stratified by early (from delivery to 6 months postpartum) and late (from 6 months to 6 years postpartum) follow-up. We performed analyses for the combined

outcome defined both by prescription data or psychiatric diagnoses (either outcome) as well as each of these outcomes separately (ignoring the other outcome).

Further, we examined the influence of PPWR on the risk of depression or anxiety with follow-up starting 6 months postpartum. This analysis was restricted to women in the cohort with information on PPWR ($n=52\,787$).

The analyses were adjusted for the following *a priori* selected covariates: Maternal age at conception (< 20, 20–24, 25–29, 30–34, 35–39, 40+ years), smoking status during pregnancy and the first 6 months postpartum (non-smoking, smoking cessation (any-time during this period), smoking), social status defined by education and occupation (low, middle, high) (Kirkegaard et al., 2014; Nohr et al., 2005), parity (0, 1, 2–3, 4+), leisure-time exercise during pregnancy (no exercise, 1–180 min/wk, > 180 min/wk), and calendar year. In the analysis of PPWR, we also adjusted for prepregnancy BMI.

2.4. Supplementary and sensitivity analyses

We tested for effect measure modification between prepregnancy BMI and PPWR on depression/anxiety by adding an interaction term between the two in the model. Also, to illustrate the combined association of prepregnancy BMI and PPWR with depression or anxiety, we computed the HR for each category in a cross-classification of prepregnancy BMI by PPWR. In that analysis, normal-weight women with no weight change from prepregnancy to 6 months postpartum served as reference.

We repeated the analysis of prepregnancy BMI restricted to women with information on PPWR only and, lastly, we restricted the analyses to primiparous women to assess whether previous pregnancies influenced the observed associations.

All analyses were performed using Stata 11.0 (StatCorp, College Station, TX, USA).

3. Ethical approval

According to Danish law, ethical approval is not required for registry-based studies (Thygesen et al., 2011). The study was approved by the Danish Data Protection Agency.

4. Results

The final study cohort consisted of 70 355 eligible mothers. Prior to pregnancy, 4% of the mothers were categorised as underweight, 68% as normal-weight, 19% as overweight, and 8% as obese. Almost half of the sub cohort with information on PPWR had changed their weight with more than one BMI unit 6 months after delivery; 14% had lost > 1 BMI unit and 34% had gained ≥ 1 BMI unit. Compared to mothers with prepregnancy BMI < 25, those with BMI ≥ 25 were more likely to have reduced their weight 6 months postpartum. Underweight women and women with BMI ≥ 25 were less likely to have a high social status and to do leisure-time exercise in pregnancy than normal-weight women. During pregnancy and early motherhood, the percentage of smokers was highest in the underweight women (Table 1). Median follow-up time for the study population was 3.9 years (IQR 1.9–6.0).

We identified 4272 incident cases of depression and/or anxiety (6.1%) from time of delivery and during follow-up. The incidence of depression and/or anxiety in the BMI groups during follow-up was 8.2% for the underweight mothers, 5.8% for the normal-weight mothers, and 6.2% and 7.3% for the overweight and obese mothers, respectively.

The cumulative HR of depression or anxiety by prepregnancy BMI was significantly increased for both underweight and overweight/obese mothers compared to normal-weight mothers (Fig. 1). To be noted, the cumulative HR's indicated in Fig. 1 are higher than the incidence rates described above because the cumulative HR is calculated based on the actual time each woman is represented in the study.

The crude analysis indicated a u-shaped association between prepregnancy BMI and depression and/or anxiety with the highest risk for underweight mothers. The HR's were 1.40, 1.04, and 1.20 for underweight, overweight, and obese, respectively, compared to normal-weight women (Table 2). After adjustment, these associations were attenuated and remained only statistically significant for underweight mothers.

In the analysis stratified by time period, the early period with only a limited number of cases from delivery to 6 months postpartum ($n=316$) showed no significant association between prepregnancy BMI and risk of depression or anxiety but the estimates were in accord with the overall analysis. The estimates in the latter time period yielded equivalent estimates as seen for the analysis of the entire time period.

Compared to women who had returned to their prepregnancy BMI, the crude analysis of PPWR showed that both positive and negative weight changes were associated with an increased risk of depression or anxiety in incident cases from 6 months postpartum until the end of follow-up. After adjustments, these associations remained and indicated again a u-shaped association with an increasing risk for depression/anxiety for mothers that lost more than 1 BMI unit (HR 1.19 (95% CI 1.06–1.34)) and mothers that gained 2–3 BMI units (HR 1.23 (95% CI 1.08–4.0)) or 3+ BMI units (HR 1.21 (95% CI 1.05–1.40)) compared to mothers who returned to their prepregnancy BMI (Table 3).

We did not observe any significant deviation from the multiplicative scale between prepregnancy BMI and PPWR ($p=0.31$). The HR of each category of prepregnancy BMI by PPWR did not deviate much from the overall analysis in normal-weight and overweight mothers (Table 4). However, for underweight and obese women, the associations between pregnancy-related weight change and depression and/or anxiety were slightly stronger than in the overall analysis. Restricting the analyses to primiparous women, showed similar results as the analyses in the full cohort (Supplemental Tables 1–3).

5. Discussion

We observed a moderate u-shaped association between prepregnancy BMI and depression/anxiety from delivery to 6 years postpartum with lowest risk for those mothers with normal BMI and PPWR. This association was attenuated after adjustments. Mothers who had lost weight or gained ≥ 2 BMI units 6 months after delivery compared to their prepregnancy BMI had a small but consistent increased risk of depression/anxiety in the following years. This association was present in all sub categories of BMI.

Why obesity, weight gain and poor mental health are associated is not well understood but several causal pathways have been proposed (Luppino et al., 2010; Penninx et al., 2013). Some studies suggest that the causal directions can go both ways. Weight gain and obesity may increase the risk of poor mental health and vice versa (Kontinen et al., 2013; Luppino et al., 2010; Penninx et al., 2013; Soczynska et al., 2011). Biological mechanisms related to inflammation, dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis and metabolic changes may be implicated in a causal pathway (Hryhorczuk et al., 2013; Luppino et al., 2010; Penninx et al., 2013; Soczynska et al., 2011). Furthermore, common genetic risks for both conditions have also been

Table 1
Maternal characteristics by prepregnancy body mass index for 70 355 women in the Danish.

National Birth Cohort					
	All (n=70 355)	Underweight (n=3057)	Normal-weight (n=47 936) %	Overweight (n=13 692)	Obese (n=5670)
Weight change (BMI units) *					
> 1 loss	14.4	3.7	10.1	21.8	39.9
–1– < 1	51.7	60.9	55.5	43.1	35.9
1– < 2	19.0	21.4	20.1	17.4	11.3
2– < 3	8.3	8.3	8.5	8.9	5.6
3+	6.6	5.7	5.9	8.7	7.4
Age of conception (years)					
< 20	1.0	2.4	1.0	0.8	1.3
20–24	12.4	15.8	11.3	13.7	15.9
25–29	42.8	43.1	42.8	42.6	42.6
30–34	33.3	30.1	33.9	32.5	31.4
35–39	9.7	8.1	10.0	9.5	8.3
40+	0.9	0.6	1.0	0.9	0.6
Parity					
0	50.7	49.2	51.8	48.3	47.8
1	34.6	36.9	33.8	36.2	36.2
2–3	14.3	13.4	14.0	15.0	15.2
4+	0.4	0.4	0.4	0.5	0.8
Social status					
Low	8.1	10.9	6.9	9.4	14.1
Middle	36.4	38.1	33.9	41.3	45.0
High	51.7	45.7	55.9	45.2	35.2
Smoking in pregnancy					
Non smoking	57.6	48.0	57.6	58.7	59.8
Smoking cessation	6.8	7.3	7.0	6.7	5.8
Smoking	13.2	19.4	12.5	13.3	14.9
Exercise in pregnancy (min/wk)					
None	62.2	66.9	60.5	64.5	67.9
1–179	29.8	25.0	30.7	28.9	26.6
180+	8.0	7.9	8.7	6.4	5.3
* Known information on weight change	(n=52 787)	(n=2236)	(n=36 130)	(n=10 269)	(n=4152)
In per cent	75.0	73.1	75.4	75.0	73.2

Columns do not add up to 100% due to missing data.

suggested as an explanation of the observed associations (Afar et al., 2010). Finally, psychological factors such as poor self-esteem and body image may be related to obesity and also affect mental health (Garipey et al., 2010; Molyneaux et al., 2014; Peter et al., 2014).

An association between obesity and poor mental health in the general population has been reported (Atlantis et al., 2005). A Dutch cross-sectional study of 43 534 adult men and women found the association between BMI and depression to be u-shaped similar to what we saw which corresponds with findings by Lacoursiere et al. (2006). They examined the association between maternal BMI and self-reported postpartum depressive symptoms and found normal-weight women less likely to report moderate or greater depressive symptoms. Reports on the associations between prepregnancy BMI and later symptoms of depression or anxiety stem from smaller studies indicating an increased risk with high BMI (Carter et al., 2000; LaCoursiere et al., 2010). These studies rely on self-reported symptoms (Lacoursiere et al., 2006) or they used different screening tools (the Edinburgh Postnatal Depression Scale, LaCoursiere et al., 2010 or the CES-D Carter et al., 2000) but none of these studies examined the association beyond 14 months after delivery. Woolhouse et al. (2014) examined the point prevalence of maternal depression repeatedly from three months postpartum till four years postpartum. Their findings suggest, unexpectedly, that the risk of depression was highest four years after delivery, indicating a need for long follow-up periods when studying maternal depression.

Pregnancy-related weight retention and the correlated increase in BMI may be difficult to accept for women with a high degree of

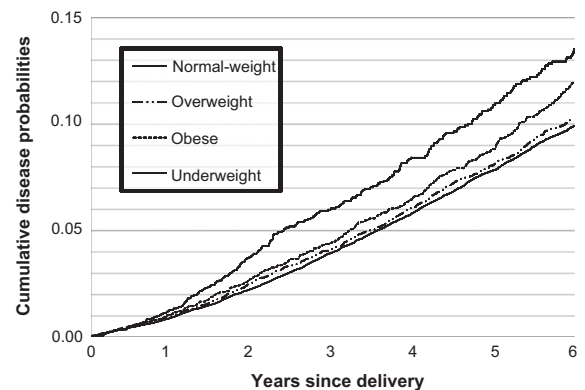


Fig. 1. Nelson-Aalen cumulative hazard rates for depression or anxiety (diagnosis or prescription) by prepregnancy BMI. The Danish National Birth Cohort.

body awareness, particularly if the added weight remains beyond the first 6 to 12 months. We estimated the risk of new cases of depression/anxiety and our results suggest that PPWR impact the mental wellbeing of the mother in the years following childbirth. However, Pedersen et al. (2011) found that mothers with incident cases of depression during pregnancy or at 6 months postpartum had substantial weight retention 6 and 18 months after delivery, suggesting that pregnancy- and childbirth-related depression may be a barrier to resuming prepregnancy BMI and a cause of obesity. Herring et al. (2008) only found this for only for newly-onset postpartum depression and not for antenatal depression.

Table 2
Hazard ratios (HR) for depression and/or anxiety according to prepregnancy body mass index. The Danish National Birth Cohort.

	Person years	Events	HR (crude)	(95% CI)	HR*	(95% CI)
Full period (delivery to 6 years postpartum)						
Depression or anxiety (presc. or diagnosis)						
BMI < 18.5	13196	251	1.40	(1.23–1.60)	1.24	(1.06–1.45)
BMI 18.5– < 25	204503	2756	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	60002	851	1.04	(0.96–1.13)	1.05	(0.96–1.15)
BMI 30+	25273	414	1.20	(1.08–1.33)	1.07	(0.95–1.21)
Depression or anxiety (only prescriptions)						
BMI < 18.5	13216	241	1.40	(1.23–1.60)	1.23	(1.05–1.44)
BMI 18.5– < 25	204791	2656	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	60095	815	1.04	(0.96–1.12)	1.03	(0.94–1.13)
BMI 30+	25305	401	1.20	(1.08–1.33)	1.08	(0.95–1.22)
Depression or anxiety (only diagnosis)						
BMI < 18.5	13744	45	1.61	(1.19–2.19)	1.29	(0.87–1.90)
BMI 18.5– < 25	210354	424	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	61741	150	1.19	(0.99–1.44)	1.21	(0.97–1.51)
BMI 30+	26113	67	1.25	(0.97–1.62)	1.02	(0.74–1.40)
Early period (delivery to 6 months postpartum)						
Depression or anxiety (presc. or diagnosis)						
BMI < 18.5	1501	16	1.21	(0.73–2.01)	1.02	(0.54–1.94)
BMI 18.5– < 25	23557	208	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	6725	64	1.08	(0.81–1.43)	1.07	(0.77–1.49)
BMI 30+	2782	28	1.14	(0.77–1.69)	1.20	(0.77–1.87)
Depression or anxiety (only prescriptions)						
BMI < 18.5	1502	14	1.21	(0.70–2.09)	1.03	(0.52–2.03)
BMI 18.5– < 25	23566	181	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	6726	59	1.14	(0.85–1.53)	1.09	(0.76–1.54)
BMI 30+	2783	25	1.17	(0.77–1.78)	1.29	(0.82–2.04)
Depression or anxiety (only diagnosis)						
BMI < 18.5	1503	4	1.01	(0.37–2.78)	1.05	(0.32–3.40)
BMI 18.5– < 25	23588	62	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	6736	19	1.07	(0.64–1.79)	1.29	(0.72–2.29)
BMI 30+	2786	9	1.23	(0.61–2.47)	1.14	(0.48–2.70)
Late period (6 months to 6 years postpartum)						
Depression or anxiety (presc. or diagnosis)						
BMI < 18.5	11695	235	1.42	(1.24–1.62)	1.25	(1.07–1.47)
BMI 18.5– < 25	180946	2548	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	53277	787	1.04	(0.96–1.13)	1.05	(0.95–1.15)
BMI 30+	22491	386	1.20	(1.08–1.34)	1.06	(0.93–1.21)
Depression or anxiety (only prescriptions)						
BMI < 18.5	11714	227	1.41	(1.23–1.62)	1.24	(1.05–1.46)
BMI 18.5– < 25	181225	2475	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	53369	756	1.03	(0.95–1.11)	1.03	(0.94–1.13)
BMI 30+	22522	376	1.20	(1.08–1.34)	1.06	(0.93–1.21)
Depression or anxiety (only diagnosis)						
BMI < 18.5	12241	41	1.71	(1.24–2.36)	1.32	(0.88–2.00)
BMI 18.5– < 25	186766	362	1.00	(Ref.)	1.00	(Ref.)
BMI 25– < 30	55005	131	1.21	(0.99–1.48)	1.20	(0.95–1.52)
BMI 30+	23326	58	1.25	(0.95–1.65)	1.01	(0.71–1.42)

Results are reported for prescriptions or diagnosis (either outcome), and for each of these separately (ignoring the other outcome). Thus, for the latter, some cases might be presented in both groups.

* Adjusted for age at conception, parity, social status, smoking and exercise in pregnancy, and calendar year.

Furthermore, studies investigating predictors for PPWR have found stress and abnormal sleeping patterns to be potential indicators of PPWR (Siega-Riz et al., 2010; Whitaker et al., 2014). Milder stress, a condition that shares many risk factors and symptoms with depression, is often associated with weight gain. It is therefore difficult to disentangle the proper time sequence: mental distress in early motherhood leading to PPWR or PPWR affecting mental disorders.

Whether it is the BMI change from prepregnancy or the resultant BMI that drives the association between PPWR and risk of depression/anxiety is open for discussion. Our results suggest that it may be the weight retention after childbirth that is the main driver as the association between PPWR and risk of depression/anxiety was seen for all strata of prepregnancy BMI. However, the association with PPWR seemed to be stronger for mothers who were either underweight or obese prior to conception perhaps

related to a higher mental vulnerability to weight retention in these groups of women.

Depression and anxiety was examined as a combined outcome because anxiety has been related to BMI and PPWR in a similar way as depression (Bogaerts et al., 2013; Molyneaux et al., 2014). Hence, we found it reasonable to make a composite endpoint. The use of prescription data as one of the outcomes made it difficult to disentangle the two disorders because of the considerable overlap in the medical treatment for depression and anxiety.

As gestational weight gain is closely associated with PPWR (Ashley-Martin and Woolcott, 2014; Linne et al., 2004; Mannan et al., 2013), gestational weight gain could also have been chosen as the exposure. However, we believe PPWR to be a more specific indicator of long term overweight since gestational weight gain is a more pregnancy-related measure closely related to birth weight and gestational length.

Table 3

Hazard ratios (HR) for depression and/or anxiety according to postpartum weight retention (PPWR) from 6 months to 6 years postpartum (The Danish National Birth Cohort).

	Person years	Events	HR (crude)	(95% CI)	HR ^a	(95% CI)
From six months till six years postpartum						
Depression or anxiety (presc. or diagnosis)						
Loss of > 1 BMI	28725	480	1.32	(1.19–1.46)	1.19	(1.06–1.34)
– 1– < 1 BMI	104990	1335	1.00	(Ref.)	1.00	(Ref.)
1– < 2 BMI	38550	528	1.08	(0.97–1.19)	1.05	(0.94–1.16)
2– < 3 BMI	16617	284	1.35	(1.18–1.53)	1.23	(1.07–1.40)
3+ BMI	12933	251	1.53	(1.34–1.75)	1.21	(1.05–1.40)
Depression or anxiety (only prescription)						
Loss of > 1 BMI	28804	460	1.29	(1.16–1.44)	1.16	(1.03–1.30)
– 1– < 1 BMI	105116	1305	1.00	(Ref.)	1.00	(Ref.)
1– < 2 BMI	38598	507	1.06	(0.95–1.17)	1.02	(0.92–1.14)
2– < 3 BMI	16653	273	1.32	(1.16–1.51)	1.20	(1.05–1.37)
3+ BMI	12956	244	1.52	(1.33–1.75)	1.20	(1.04–1.39)
Depression or anxiety (only diagnosis)						
Loss of > 1 BMI	29796	81	1.57	(1.21–2.04)	1.45	(1.09–1.93)
– 1– < 1 BMI	108012	187	1.00	(Ref.)	1.00	(Ref.)
1– < 2 BMI	39735	77	1.12	(0.86–1.46)	1.08	(0.82–1.43)
2– < 3 BMI	17183	48	1.61	(1.17–2.21)	1.45	(1.04–2.02)
3+ BMI	13498	43	1.84	(1.32–2.57)	1.51	(1.06–2.15)

^a Adjusted for prepregnancy BMI, age at conception, parity, social status, smoking and exercise in pregnancy, and calendar year.

Table 4

Hazard ratios (HR) for cross-classification of prepregnancy BMI and postpartum weight retention on risk of depression and/or anxiety from 6 months to 6 years postpartum in the Danish National Birth Cohort.

Pregnancy BMI	Postpartum weight retention (BMI units)									
	Loss > 1	(95% CI)	– 1– < 1	(95% CI)	1– < 2	(95% CI)	2– < 3	(95% CI)	3+	(95% CI)
Underweight	1.75	(0.87–3.52)	1.21	(0.97–1.51)	1.35	(0.95–1.91)	2.03	(1.30–3.16)	1.35	(0.74–2.45)
Normal-weight	1.27	(1.09–1.48)	1.00	(ref.)	0.99	(0.87–1.13)	1.16	(0.99–1.37)	1.24	(1.03–1.49)
Overweight	1.11	(0.91–1.34)	1.04	(0.90–1.21)	1.13	(0.91–1.39)	1.21	(0.92–1.59)	1.24	(0.95–1.62)
Obese	1.21	(0.98–1.48)	0.96	(0.75–1.22)	1.46	(1.05–2.04)	1.77	(1.14–2.76)	1.11	(0.71–1.74)
All ^a	1.19	(1.06–1.34)	1.00	(ref.)	1.05	(0.94–1.16)	1.23	(1.07–1.40)	1.21	(1.05–1.40)

Adjusted for age at conception, parity, social status, smoking and exercise in pregnancy and calendar year.

Reference woman: Prepregnancy normal-weight woman with weight gain between – 1 < 1 from prepregnancy BMI until six months postpartum.

N=52 787 mothers.

^a Also adjusted for prepregnancy BMI.

5.1. Strengths and limitations

Our study is based on a large pregnancy cohort with extensive information on potential confounders and exposure information was collected prospectively reducing the risk of differentiated recall. The linkage with individual data from the Danish national registries is a key strength as these registries have a high degree of completeness for those admitted to hospitals (Kildemoes et al., 2011; Lyngé et al., 2011; Mors et al., 2011) and hence allow for almost complete follow-up.

Certain limitations of this study need also to be mentioned. Data on exposure was self-reported both regarding prepregnancy BMI and BMI 6 months after delivery. Self-reported prepregnancy BMI has been validated relative to prepregnancy BMI reported by the general practitioner at approximately 9th week of gestation in a sub-cohort from the DNBC of 5033 women. Agreement on BMI category was found for about 90% (Nohr, 2005).

We only included mothers from the DNBC who gave information on prepregnancy weight and height, and for the analysis including PPWR also weight 6 months after delivery. Only few mothers were excluded due to missing information on prepregnancy BMI. For PPWR, we compared mother who gave information on weight 6 months postpartum and those who did not, and the two groups had similar risk of mental disorder.

Unfortunately, only hospital treated mental disorders are available in the Danish Psychiatric Central Research Register and the NPR as most patients with a mild to moderate mental disorder are

diagnosed and treated by general practitioners or private practicing psychiatrists or psychologists. As for severe mental disorders, the nationwide registration in the Danish Psychiatric Research Register is nearly complete (Mors et al., 2011), however, the diagnoses in the Danish Psychiatric Research Register have not been systematically validated. Bock et al. (2009) found diagnoses of a single depressive episode to have good precision. In the Danish National Prescription Registry, the indication for the prescription is not given. However, by combining diagnoses with prescription data, using a redeemed prescription of antidepressant as a proxy for a diagnosis of depression or anxiety, we probably cover most diagnoses of depression or anxiety in our follow-up period. It is to be noted however, that by making the definition of cases dependent of attention of medical services, there is a small risk of differential misclassification that may lead to bias in both directions. For instance, if a woman is underweight or has lost substantial weight in the postnatal period, her GP may be more likely to ask about her mental wellbeing and if so, we risk an overestimation of the association.

Diagnoses, given by a GP or private practice psychiatrist or psychologist without providing treatment with SSRIs or other antidepressants, are not included in our data. Further, antidepressants might be prescribed for conditions other than depression or anxiety. We expect that such underreporting and misclassification of cases due to untreated disorders and misclassification of mental diagnoses would not be related to BMI or PPWR and will most likely bias results towards the null.

We excluded mothers with prior redemption of any antidepressant or diagnosis of any mental disorder but we cannot completely remove the risk of prevalent untreated/undiagnosed cases of disorder prior to start of follow-up. Particularly, when PPWR was the exposure, the pregnancy-related weight change from conception to 6 months postpartum – both loss and gain – might be influenced by mental disorder evolving in this time period rather than PPWR causing mental disorders (Herring et al., 2008; Pedersen et al., 2011; Whitaker et al., 2014).

6. Conclusion

In conclusion, we found that being underweight prior to pregnancy increased the risk of depression/anxiety disorders from delivery to 6 years postpartum. PPWR 6 months after delivery displayed an association with depression and/or anxiety. This association was seen in all BMI groups. The findings of this study support the health benefits of entering pregnancy as normal-weight and to return to ones prepregnancy BMI afterwards. Finally, identification of prepregnancy BMI and PPWR as predictors of depression or anxiety disorders requiring treatment may help healthcare workers to prevent these disorders.

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Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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Appendix A

We excluded mothers that had redeemed one of the following drugs prior to start of follow-up: N05A (Antipsychotics), N05BA (Phenothiazines with piperazine structure), N05CD (Benzodiazepine derivatives), N05CF (Benzodiazepine related drugs), N06AA (Non-selective monoamine reuptake inhibitors including tricyclic antidepressants (TCA), N06AB (Selective serotonin reuptake

inhibitors), N06AX (Selective serotonin reuptake inhibitors), and N06BA (Centrally acting sympathomimetics).

Furthermore, we excluded mothers diagnosed with an ICD8 codes 295 (Schizophrenia), 296 (Affective psychoses), 297 (Paranoid status), 298 (Other psychoses), 299 (Unspecified psychoses), or 300 (Neuroses) (1977–1993), or any ICD10 codes F00–99 (Mental and behavioural disorders) in the NPR or in the Danish Psychiatric Research Register prior to start of follow-up.

Appendix B. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jad.2015.04.053>.

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