Owe, K. M., Støer, N., Wold, B. H., Magnus, M. C., Nystad, W., & Vikanes, Å. V. (2019). Leisure-time physical activity before pregnancy and risk of hyperemesis gravidarum: a population-based cohort study. *Preventive Medicine*, *125*, 49-54. https://doi.org/10.1016/j.ypmed.2019.05.002

Accepted Manuscript

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PII: S0091-7435(19)30170-7
DOI: https://doi.org/10.1016/j.ypmed.2019.05.002
Reference: YPMED 5714

To appear in: *Preventive Medicine*

Received date: 12 October 2018
Revised date: 2 May 2019
Accepted date: 7 May 2019

Please cite this article as: K.M. Owe, N. Støer, B.H. Wold, et al., Leisure-time physical activity before pregnancy and risk of hyperemesis gravidarum: a population-based cohort study, Preventive Medicine, https://doi.org/10.1016/j.ypmed.2019.05.002

Leisure-time physical activity before pregnancy and risk of hyperemesis gravidarum: a population-based cohort study

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Conflicts of interest: The authors have stated explicitly that there are no conflict of interest in connection with this article.

Short version of title: Physical activity before pregnancy and hyperemesis gravidarum

Word count of abstract: 249.

Word count of main text: 3048.

Tables: 3.

Figures: 2

ABSTRACT

Introduction: Women who experience severe nausea and vomiting in early pregnancy are less likely to participate in leisure-time physical activity (LTPA) during pregnancy. Whether LTPA before pregnancy is associated with hyperemesis gravidarum (HG) has not yet been studied. The aim of the study was to estimate associations between prepregnancy LTPA and HG in pregnancy. Methods: We present data from 37 442 primiparous women with singleton pregnancies enrolled in The Norwegian Mother and Child Cohort Study. Prepregnancy LTPA was self-reported by questionnaire in pregnancy week 17. HG was reported in week 30 and defined as prolonged nausea and vomiting in pregnancy requiring hospitalisation before the 25^{th} gestational week. We estimated the crude and adjusted associations between LTPA and HG using multiple logistic regression. We assessed effect modification by prepregnancy BMI or smoking by stratified analysis and interaction terms. Results: A total of 398 (1.1%) women developed HG. Before pregnancy 56.7% conducted LTPA at least 3 times weekly, while 18.4% of women conducted LTPA less than once a week. Compared to women reporting LTPA 3 to 5 times weekly, women reporting no LTPA before pregnancy had an increased odds of HG (adjusted odds ratio [aOR] 1.69; 95% confidence interval [CI], 1.20 to 2.37). LTPA-HG associations differed by prepregnancy BMI but not by prepregnancy smoking. Discussion: Lack of LTPA before pregnancy was associated with an increased odds of HG. Due to few cases of HG and thereby low statistical power, one need to be cautious when interpreting the results of this study.

Key-words: The Norwegian Mother and Child Cohort Study, MoBa, hyperemesis gravidarum, physical activity, pregnancy, prevention; pregnancy complications.

Introduction

Hyperemesis gravidarum (HG) is characterised by excessive nausea and vomiting starting before the 22nd week of gestation, often leading to maternal weight loss, dehydration, electrolyte imbalance and vitamin deficiencies [1]. The prevalence of HG differs depending on maternal country of birth and it is the most common reason for hospitalisation in early pregnancy [2 3]. In Norway, between 0.8 and 3.2% women develop HG. Women born in Norway have the lowest prevalence whereas the highest prevalence of HG is observed among women born in India and Sub-Saharan Africa [4]. The etiology of HG remains unknown but both genetic and lifestyle factors are likely to play a role [5].

HG is more common in non-smoking women and among women who are underweight or overweight [6] and in women with a diet high on saturated fat [7]. In contrast, smokers and women with a high intake of fish, seafood and a moderate intake of water before pregnancy may have a lower risk of HG [8-10]. Whether other life style factors, such as leisure-time physical activity (LTPA) are associated with the development of HG, has not yet been studied. It is, however, well known that LTPA before pregnancy reduces the risk of other pregnancy-related conditions, such as gestational diabetes [11], pelvic girdle pain [12], and hypertensive disorders including preeclampsia [13 14]. These conditions are all previously reported to be associated with HG [15-18]. Given that women experiencing severe nausea and vomiting in early pregnancy are less likely to participate in LTPA during pregnancy [19], the aim of this study was to explore if LTPA before pregnancy is associated with the risk of HG.

Material and methods

This study is based on data from MoBa, a large population-based prospective pregnancy cohort administered by the Norwegian Institute of Public Health. All pregnant women scheduled to give birth at 50 hospitals in Norway, were targeted for recruitment between 1999 and 2008, and the cohort includes 95 000 mothers and 114 000 children [20]. Routines for recruitment are described elsewhere [20 21]. Follow up is conducted by questionnaires at regular intervals and by linkage to national health registries. The current study is based on version VIII of the quality-assured data files released for research in 2014. Written informed consent was obtained from all participants upon recruitment. The study was approved by The Regional Committee for Medical Research Ethics in South-East Norway.

The study population included primiparous MoBa participants who gave birth to a singleton and who had answered the questionnaires administered at pregnancy weeks 17 and 30 gestational weeks (48 463 eligible women). We included primiparous women only due to the high recurrence risk of HG in a subsequent pregnancy[22] and the observation that multiparous women have a higher BMI. We excluded women who did not answer both questionnaires in pregnancy (n=7046), women who responded to the first version of the two questionnaires at weeks 17 and 30 due to dissimilar questions on physical activity (n=1 753). We also omitted women with missing data on one or more variables in the analysis (n=2222). This left 37 442 women who were included in the study (Figure 1). Given that early onset of HG would negatively impact on LTPA levels in mid pregnancy, we aimed to study the association between prepregnancy LTPA and HG in pregnant primiparous women. MoBa was linked to the Medical Birth Registry of Norway (MBRN).

The main outcome is hyperemesis gravidarum (HG), defined as prolonged nausea and vomiting in pregnancy that requires hospitalization before the 25th week of pregnancy, as reported in pregnancy week 30. HG was dichotomised into “no” and “yes”.

The exposure of interest was self-reported frequency of leisure-time physical activity (LTPA) three months before pregnancy. In pregnancy week 17, women were asked how often they had performed the following 14 activities during the last three months before pregnancy: strolling, brisk walking, running (jogging or orienteering), bicycling, training in fitness centres, prenatal aerobic classes, low impact aerobic classes, high impact aerobic classes, dancing (swing, rock, folkdance), skiing, ball games, swimming, horseback riding, and other. To avoid overestimated proportions of women being physically active, we defined women who only reported strolling as physically inactive. For each activity, the following predefined frequencies were given: “never”, “1-3 times per month”, “once a week”, “twice a week” and “≥3 times per week”. In order to estimate the total frequency of LTPA, the frequency for each category was calculated. Frequencies of LTPA were then combined into five categories: “Never” (strolling and never), “1-3 times per month”, “1-2 times per week”, “3-5 times per week” and “≥ 6 times per week”.

We considered covariates known to be associated with prepregnancy LTPA and HG as potential confounders. The following covariates were included; maternal age at delivery (<20, 20-24, 25-29, 30-34 and ≥ 35 years old), smoking habits before pregnancy (never, occasionally, and daily), length of education (<12, 12, 13-15 and ≥16 years), and prepregnancy body mass index ((BMI), underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9) and obese (≥30.0 kg/m).

Statistical analysis

We used multiple logistic regression analysis to estimate the associations between frequency of prepregnancy LTPA and HG, and present crude (cORs) and adjusted (aORs) odds ratios with 95% confidence intervals (CI). LTPA 3 to 5 times per week was used as reference category. The final model was adjusted for maternal age, prepregnancy BMI, length of education, and prepregnancy smoking.

LTPA during pregnancy is partly dependent of prepregnancy LTPA and may at the same time correlate with HG. Hence, it is not included in the adjusted model. We evaluated the presence of multiplicative interaction of smoking and prepregnancy BMI on the association between LTPA and HG by including product terms in the models. A comparison of models with and without interaction terms were carried out with likelihood ratio tests. We also assessed p-values for trend in risk of HG according to the increasing frequency of LTPA. To account for the non-linear associations between prepregnancy LTPA and HG risk, prepregnancy LTPA was modelled using restricted cubic splines with four knots at fixed percentiles of the distribution [23]. We also added a rug plot on the x-axis to illustrate the distribution of prepregnancy LTPA. Data were analysed with R version 3.1.1 (http://cran.r-project.org) and Stata version 15.1 (StataCorp, College Station, TX, USA).

Ethics approval

Informed, written consent was obtained from the participants upon recruitment. The Norwegian Mother and Child Cohort Study was approved by the Regional Committee for Ethics in Medical Research in South-Eastern Norway and the Norwegian Data Inspectorate, (Reference number S-97045 and 01/4325, respectively).

RESULTS

Among the participating women, 398 (1.1%) had HG. More than half of the women reported LTPA at least three times weekly before pregnancy (21607 out of 37 442, 56.7%), whereas 18.4% (6906 out of 37 442) reported to be physically active less than once a week. The latter group of women were younger, had less education and were more likely to smoke in addition to having BMI lower than 18.5 kg/m^2 or higher than 25.0 kg/m^2 (Table 1). The proportion of women with HG was 1.9% among those reporting no LTPA before pregnancy compared to 0.9% among women reporting LTPA 3-5 times a week (Table 2).

When modelling prepregnancy LTPA by restricted cubic splines, we observed a non-linear association (Figure 2). The shape of the curve revealed an increased odds of HG at the lower end of the distribution with the highest odds among women reporting no LTPA before pregnancy (Figure 2). The association between frequency of prepregnancy LTPA and HG is shown in Table 2. Women who reported no LTPA before pregnancy had twice the odds of HG compared to women reporting LTPA 3 to 5 times per week (cOR 2.17; 95% CI 1.56 to 3.03). Adjustment for potential confounders attenuated the observed association (aOR 1.69; 1.20 to 2.37). Women reporting LTPA 1 to 3 times monthly were also more likely to develop HG (cOR 1.41; 1.102 to 1.94, test for trend, P=0.01). After adjusting for potential confounders, the association was no longer statistical significant (aOR 1.17; 0.85 to 1.63, test for trend, P=0.21).

Overall test for interaction between frequencies of prepregnancy LTPA and BMI was not significant (P=0.10). However specific tests for interactions was significant for “LPTA 1 to 3 times a month” (P=0.03). We therefore also present associations between prepregnancy LTPA and HG according to maternal overweight/obesity status ($25 \geq$ BMI < 25 kg/m^2) (Table 3). Women with BMI < 25kg/m^2 reporting no LTPA or LTPA 1 to 3 times a month had an increased odds of HG (cOR 2.64; 1.74 to 4.01, and 1.85; 1.25-2.74, respectively, Test for trend, P=0.01) compared to LTPA 3 to 5 times a week. Even though adjusting for maternal age, education and prepregnancy smoking attenuated the effect estimates, no LTPA was still associated with a 2-fold increased odds of HG. We also observed a non-linear association between prepregnancy LTPA and HG in women with BMI ≥ 25 kg/m^2 (n=10 689) (not shown). Although not statistically significant, prepregnancy LTPA 1 to 3 times a month was associated with a lower odds of HG in women with overweight and obesity (cOR 0.80; 0.45 to 1.41). The adjusted effect estimates were essentially the same.

Test for interaction between prepregnancy smoking and LTPA was not statistically significant (P-value= 0.13).

Discussion

This is the first study to explore if leisure-time physical activity (LTPA) before pregnancy is associated with HG in pregnancy. Using data from a large prospective population-based cohort study, our findings suggest that primiparous women reporting no LTPA before pregnancy have a higher odds for HG compared to women reporting LTPA 3 to 5 times a week. For normal weight women with low levels of LTPA, the odds of HG may be even more pronounced.

Our findings are novel, and need replication. There may, however, be several potential explanations for the association between prepregnancy LTPA and HG. Together with a healthy diet, a BMI within the normal range and being a non-smoker, regular physical activity may represent a healthy lifestyle in general. These modifiable behavioural factors may in turn influence possible underlying biological mechanisms and thus reduce the risk of HG in these women [10 24 25]. Adjusting for prepregnancy BMI and smoking habits attenuated the effect estimates, particularly for women with low levels of LTPA before pregnancy. We can therefore not exclude the possibility that the observed association between LTPA before pregnancy and HG might at least partly reflect the complex relationship between lifestyle characteristics.

The association between LTPA and HG among women with a BMI <25 kg/m^2 was positive for all levels of LTPA compared to being physically active 3-5 times a week. However, only low levels of LTPA (i.e. less than once a week) was significantly associated with an increased odds of HG among normal weight women. Furthermore, there was a non-linear association between LTPA and HG among women with a prepregnancy BMI ≥ 25 kg/m^2. We observed a non-significant increased odds of HG among overweight and obese women except for a non-significant protective effect of LTPA 1-3 times a week in the same strata of women. However, we should interpret these observations with caution due to few cases of HG and wide confidence intervals in the stratified analysis.

Physical inactivity, often defined as not meeting the World Health Organization (WHO) physical activity recommendations of 150 minutes of moderate to vigorous intensity physical activity per week, is causing many non-communicable diseases [26]. We were not able to identify physical inactive women according to WHO's definition, but note that women reporting no LTPA in our study did have some characteristics in common with women at high risk for HG; i.e. young age and high BMI. Both younger women and women with a BMI above 25 kg/m^2 have higher levels of estrogen [8], hypothesised to increase the risk of HG [27]. In line with this hypothesis, physical activity is associated with reduced levels of estrogen and progesterone in premenopausal women and might thus reduce the risk of HG [28]. Other hormones possibly influenced by LTPA may also play a role. Despite our attempts to adjust for confounding factors, we cannot rule out the possibility of confounding by other unmeasured and unknown factors. Residual confounding may also have influenced the risk estimates in our study due to other behavioural factors, socioeconomic status and BMI, all of which are closely related to LTPA.

There is no international consensus on the exact definition of HG[29]. Information about metabolic disturbances which are listed as diagnostic criteria in the ICD 10th edition of the International Classification of Diseases in 1999 (ICD 10 for severe HG) was not available. Therefore we included only women hospitalised before 25th gestational week and with self-reported excessive vomiting and nausea. Although the prevalence of exposure and outcome might differ from the Norwegian population at large, the estimates are most likely considered valid [30]. The prevalence of HG in our study was 1.1% which is in line with a previous register-based study from the MBRN, reporting the overall prevalence of hyperemesis to be 0.9% among primiparous women in Norway [4]. Previous research on HG in MoBa has shown that 74% of these women were hospitalised during their 1st trimester [6]. The large proportion of non-smokers in MoBa compared to the target population [30], may partly explain the higher prevalence of HG in our study. We also observed a high proportion of smokers among the non-active women in our study, which may have attenuated the association between LTPA and HG due to the protective effect of smoking on the development of HG[31].

Self-reported and recalled information on LTPA before pregnancy may have overestimated levels of LTPA with an underestimated proportion of women not participating in any LTPA. If the latter group of women over-report their levels of LTPA it will attenuate the effect estimates. Thus the true risk of HG among physically inactive women may even be higher than our estimates. Prepregnancy LTPA was recalled in pregnancy week 17 and HG was reported in pregnancy week 30. Given that the exposure was assessed before the outcome, it is likely that any misclassification would be similar in women with and without HG. A low proportion of women in our study did not report any LTPA before pregnancy (6.9%). Hence, the absolute number of HG cases among these women was low and consequently the power to detect a true difference was weak.

The questions used to assess LTPA in our study have shown acceptable concurrent validity when compared to accelerometer in a smaller sample of pregnant women participating in the MoBa study [32]. The questionnaire did not, however, assess the intensity or duration of LTPA, and other domains of physical activity such as transportation, house work, or gardening were not included. Given that underlying mechanisms explaining the observed association between prepregnancy LTPA and HG remains unknown, a measure of total prepregnancy physical activity would probably have produced different estimates albeit in the same direction. Furthermore, we included varied types of LTPA typically reported by women comprising activities such as brisk walking, aerobic dancing and running. Women commonly report walking as physical activity; it is easily achievable and thus of importance for public health and longevity [33]. Even mild walking programs have shown to be beneficial for the prevention of excessive gestational weight gain in overweight/obese pregnant women, explained by improved glucose and insulin regulation despite its low intensity [34]. However, we defined strolling as a non-activity and other domains of physical activity was not included. If we had instead included strolling as LTPA, it would have overrated levels of LTPA with very few women reporting no or low frequencies of LTPA (data not shown).

Multiparous women constituted the highest proportion of excluded participants (n=61827 out of 110 290). Due to a high recurrence risk of HG in a subsequent pregnancy and the fact that we did not have information on previous pregnancies to multiparous women before they entered the MoBa study, we therefore excluded these women. Whether the observed associations are similar in multiparous women should be studied further. Women who did not respond to the questionnaires (1 and 3, respectively) in pregnancy were also excluded from the study population (n=7046 out of 110 290). Among women who did not respond to questionnaire 1 and therefore had missing information on LTPA prepregnancy (the exposure), we observed fewer cases of HG (0.2%). Further, among excluded women who did not respond to questionnaire 3 and had missing information on HG (the outcome), we observed a higher proportion of women reporting no LTPA or a frequency of 1 to 3 times a month (11.4% and 12.3%, respectively). If low levels of LTPA are associated with HG, it is plausible that including the latter group of women would have strengthened the association between LTPA and HG in our study.

The major strength of this study is the large study sample which made it possible to study a rare outcome, and allowed us to stratify by prepregnancy BMI. The large cohort encompassed comprehensive information on a wide range of covariates possibly related to the LTPA and HG. The prospective design may also have reduced random errors. Even though participating women had higher education, were older, included fewer immigrant women, and were more likely to be non-smokers as compared to the target population [30], MoBa was not specifically designed to study associations between LTPA and HG and thus reducing the potential for selection bias.

Ideally, from a public health perspective, women should start physical activity before getting pregnant with their first child and probably reduce their risk of developing HG. Regular physical activity may be an important component of a low cost preventive action, targeting women at risk of developing HG.

Conclusion

In summary, our results indicate that women reporting LTPA less than once a week before pregnancy had twice the odds of HG compared to women reporting LTPA three to five times a week. The association remained even after controlling for prepregnancy BMI and smoking. In stratified analyses we observed that women with a BMI within the normal range and who were not physically active had an even higher odds of developing HG in their first pregnancy. Studies with information on duration and intensity of leisure-time physical activity before pregnancy are needed to confirm our findings and further explain the association between physical activity and hyperemesis gravidarum.

Acknowledgements

We are grateful to all participating families in Norway who take part in MoBa.

Funding

The Norwegian Mother and Child Cohort Study is supported by the Norwegian Ministry of Health and the Ministry of Education and Research, NIH/NIEHS (contract no NO1-ES-75558), NIH/NINDS (grant no.1 UO1 NS 047537-01 and grant no. 2 UO1 NS047537-06A1), and the Norwegian Research Council/FUGE (grant no. 151918/S10).

Compliance with ethical standards

Disclosure of interests

All authors of this manuscript report no conflict of interest.

Figure legends

Figure 1. Flow chart of the study population (n=37 442).

Figure 2: Adjusted odds ratio of Hyperemesis gravidarum that was associated with prepregnancy LTPA among 37 442 primiparous women in the Norwegian Mother and Child Cohort study (2000-2008). Prepregnancy LTPA was modelled by resticted cubic splines with 4 knots (0, 2, 4 and 9) at percentiles 5%, 35%, 65% and 95%. The value of 4 was used as reference. Estimates were adjusted for prepregnancy BMI, prepregnancy smoking, maternal age and education**.**

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TABLE 1. Maternal characteristics of primiparous women participating in the Norwegian Mother and Child Cohort study (MoBa) by prepregnancy leisure-time physical activity (LTPA), n=37 442.

			Prepregnancy leisure-time physical activity			
	Overall (N=37 442)	Never (n=2597)	1-3 times/ month (n = 4309)	1-2 times/ week (n = 9291)	3-5 times/ week (n = 13965)	6 or more times/week (n =7280)
Age (years)						
< 20	691 (1.8)	86 (3.3)	134 (3.1)	162 (1.7)	191 (1.4)	118 (1.6)
20 – 24	6059 (16.2)	717 (27.6)	928 (21.5)	1518 (16.3)	1907 (13.7)	989 (13.6)
25 – 29	16 044 (42.9)	1004 (38.7)	1798 (41.7)	3994 (43.0)	5979 (42.8)	3269 (44.9)
30 – 34	11 365 (30.4)	582 (22.4)	1125 (26.1)	2809 (30.2)	4583 (32.8)	2266 (31.1)
35+	3283 (8.8)	208 (8.0)	324 (7.5)	808 (8.7)	1305 (9.3)	638 (8.8)
Prepregnancy BMI						
Less than 18.5	1277 (3.4)	154 (5.9)	168 (3.9)	287 (3.1)	440 (3.2)	228 (3.1)
18.5 – 24.9	25 476 (68.0)	1488 (57.3)	2597 (60.3)	6022 (64.8)	9745 (69.8)	5624 (77.3)
25 – 29.9	7512 (20.1)	581 (22.4)	951 (22.1)	2075 (22.3)	2781 (19.9)	1124 (15.4)
30 or higher	3177 (8.5)	374 (14.4)	593 (13.8)	907 (9.8)	999 (7.2)	304 (4.2)
Education						
Less than 12 yrs	2385 (6.4)	449 (17.3)	434 (10.1)	551 (5.9)	625 (4.5)	326 (4.5)
Secondary school. 12 yrs	9980 (26.7)	1101 (42.4)	1557 (36.1)	2558 (27.5)	3237 (23.2)	1527 (21.0)
College, up to 16 yrs	15 931 (42.5)	763 (29.4)	1635 (37.9)	4069 (43.8)	6248 (44.7)	3216 (44.2)
University, 16 yrs or more	9146 (24.4)	284 (10.9)	683 (15.9)	2113 (22.7)	3855 (27.6)	2211 (30.4)
Prepregnancy smoking						
Never	25 894 (69.2)	1397 (53.8)	2614 (60.7)	6365 (68.5)	10032 (71.8)	5486 (75.4)
Occasionally	4273 (11.4)	203 (7.8)	435 (10.1)	1031 (11.1)	1676 (12.0)	928 (12.7)
Daily	7275 (19.4)	997 (38.4)	1260 (29.2)	1895 (20.4)	2257 (16.2)	866 (11.9)

TABLE 2. Association between prepregnancy LTPA and hyperemesis gravidarum among primiparous women in MoBa (n=37 442).

	Hyperemesis gravidarum			
Prepregnancy LTPA	Number of women (%)	Cases (%)	cOR (95% CI)	aOR$_a$ (95% CI)
Never	2 597 (6.9)	50 (1.9)	2.17 (1.56-3.03)	1.69 (1.20-2.37)
1-3 times per month	4 309 (11.5)	54 (1.3)	1.41 (1.02-1.94)	1.17 (0.85-1.63)
1-2 times per week	9 291 (24.8)	93 (1.0)	1.12 (0.85-1.47)	1.05 (0.80-1.37)
3-5 times per week	13 965 (37.3)	125 (0.9)	1 (reference)	1 (reference)
≥ 6 times per week	7 280 (19.4)	76 (1.0)	1.17 (0.88-1.56)	1.18 (0.89-1.58)
$P_{\text{linear trend}}$			*0.01*	*0.21*

$_a$ Odds ratio adjusted for: age, prepregnancy BMI, education and prepregnancy smoking.

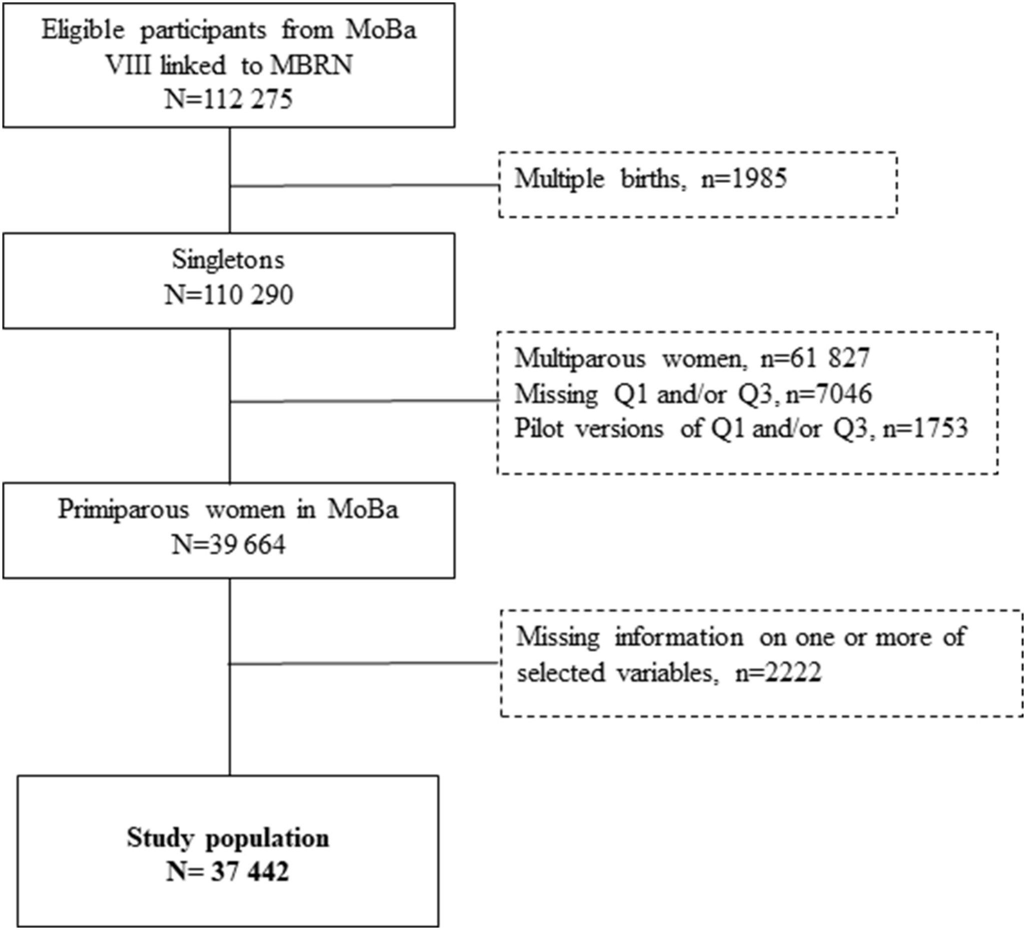
TABLE 3: Association between prepregnancy LTPA and Hyperemesis gravidarum stratified on prepregnancy BMI (25 ≥ BMI < 25 kg/m^2) in MoBa (n= 37 422).

Prepregnancy leisure-time physical activity	Hyperemesis gravidarum			
	Number of women (%)	Cases (%)	cOR (95% CI)	aOR$_a$ (95% CI)
BMI < 25 kg/m^2	26 753 (71.5)	252 (0.9)		
Never	1 642 (6.1)	32 (1.9)	2.64 (1.74 – 4.01)	2.05 (1.33-3.16)
1-3 times per month	2 765 (10.3)	38 (1.4)	1.85 (1.25 – 2.74)	1.53 (1.03-2.28)
1-2 times per week	6 309 (23.6)	54 (0.9)	1.15 (0.81-1.63)	1.07 (0.75-1.52)
3-5 times per week	10 185 (38.1)	76 (0.7)	1 (reference)	1 (reference)
≥ 6 times per week	5 852 (21.9)	52 (0.9)	1.19 (0.84-1.70)	1.17 (0.82-1.67)
$P_{linear\ trend}$			0.01	0.08
BMI ≥ 25 kg/m^2	10 689 (28.5)	146 (1.4)		
Never	955 (8.9)	18 (1.9)	1.46 (0.85-2.52)	1.31 (0.75-2.28)
1-3 times per month	1 544 (14.4)	16 (1.0)	0.80 (0.45-1.41)	0.74 (0.42-1.31)
1-2 times per week	2 982 (27.9)	39 (1.3)	1.01 (0.66-1.54)	1.01 (0.66-1.54)
3-5 times per week	3 780 (35.4)	49 (1.3)	1 (Reference)	1 (Reference)
≥ 6 times per week	1 428 (13.4)	24 (1.7)	1.30 (0.80-2.13)	1.26 (0.77-2.06)
$P_{linear\ trend}$			0.91	0.80

$_a$ Odds ratio adjusted for: age, education, and prepregnancy smoking.

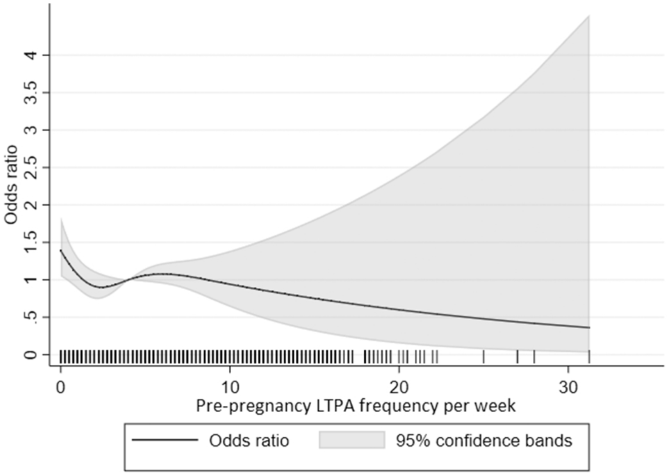
Highlights

- Prepregnancy leisure-time physical activity was associated with lower odds of HG among first-time mothers
- Prepregnancy BMI and smoking partly explained the association
- No LTPA before pregnancy was associated with more than twice the odds of HG



Eligible participants from MoBa VIII linked to MBRN
N=112 275
Multiple births, n=1985
Singletons
N=110 290
Multiparous women, n=61 827
Missing Q1 and/or Q3, n=7046
Pilot versions of Q1 and/or Q3, n=1753
Primiparous women in MoBa
N=39 664
Missing information on one or more of selected variables, n=2222
Study population
N= 37 442

Figure 1



Odds ratio
0
.5
1
1.5
2
2.5
3
3.5
4
0
10
20
30
Pre-pregnancy LTPA frequency per week
Odds ratio
95% confidence bands

Figure 2