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

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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 25th 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.

1. 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 (World Health Organization, 2011). The prevalence of HG differs depending on maternal country of birth and it is the most common reason for hospitalisation in early pregnancy (Gazmararian et al., 2002; Fiaschi et al., 2016). 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 (Vikanes et al., 2008). The etiology of HG remains unknown but both genetic and lifestyle factors are likely to play a role (Fejzo et al., 2018).

HG is more common in non-smoking women and among women who are underweight or overweight (Vikanes et al., 2010a) and in women with a diet high on saturated fat (Signorello et al., 1999). In contrast, smokers and women with a high intake of fish, seafood and a

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moderate intake of water before pregnancy may have a lower risk of HG (Vikanes et al., 2010b; Depue et al., 1987; Haugen et al., 2011). 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 (Aune et al., 2016), pelvic girdle pain (Owe et al., 2016), and hypertensive disorders including preeclampsia (Aune et al., 2014; Barakat et al., 2016). These conditions are all previously reported to be associated with HG (Kuru et al., 2012; Bolin et al., 2013; Chortatos et al., 2015; Fiaschi et al., 2018). Given that women experiencing severe nausea and vomiting in early pregnancy are less likely to participate in LTPA during pregnancy (Owe et al., 2009), the aim of this study was to explore if LTPA before pregnancy is associated with the risk of HG.

2. 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 (Magnus et al., 2016). Routines for recruitment are described elsewhere (Magnus et al., 2016; Magnus et al., 2006). 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 (48,463 eligible women). We included primiparous women only due to the high recurrence risk of HG in a subsequent pregnancy (Trogstad et al., 2005) 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 = 1753). 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 (Fig. 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 hospitalisation 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).

2.1. 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 (Orsini and Greenland, 2011). 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).

2.2. 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).

3. 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 (21,607 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 (Fig. 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 (Fig. 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

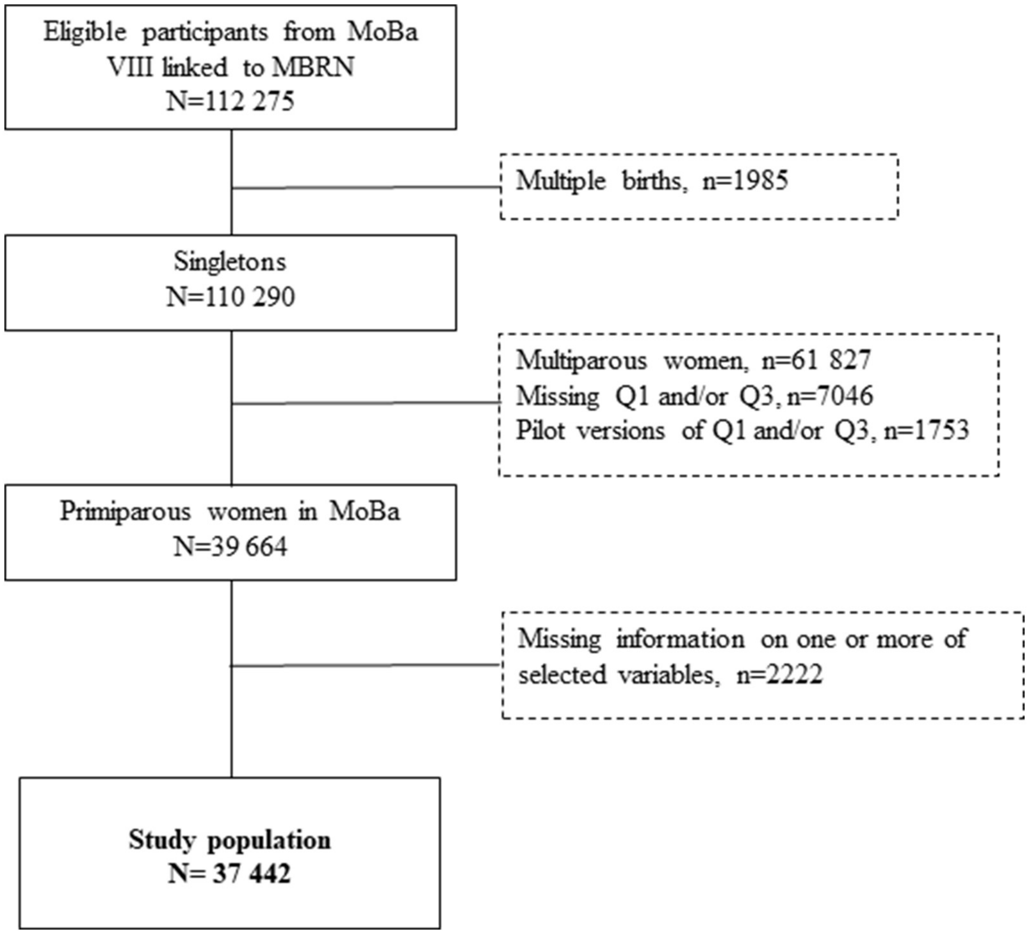

Fig. 1. Flow chart of the study population (n = 37,442).

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.

	Overall (N = 37,442)	Prepregnancy leisure-time physical activity				
		Never (n = 2597)	1–3 times/ Month (n = 4309)	1–2 times/ week (n = 9291)	3–5 times/ week (n = 13,965)	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						
< 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						
< 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)	10,032 (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	2597 (6.9)	50 (1.9)	2.17 (1.56–3.03)	1.69 (1.20–2.37)
1–3 times per month	4309 (11.5)	54 (1.3)	1.41 (1.02–1.94)	1.17 (0.85–1.63)
1–2 times per week	9291 (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	7280 (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.

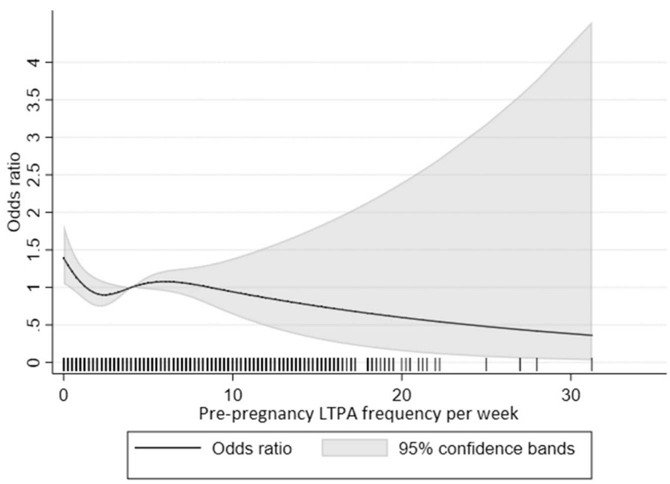

Fig. 2. Adjusted odds ratio of Hyperemesis gravidarum that was associated with prepregnancy LTPA among 37,442 primiparous women in the Norwegian Mother and Child Cohort study (2000–2008). Prepregnancy LTPA was modelled by resticted cubic splines with 4 knots (0, 2, 4 and 9) at percentiles 5%, 35%, 65%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

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 ($25 \geq \text{BMI} < 25\,\text{kg/m}^2$) (Table 3). Women with BMI $< 25\,\text{kg/m}^2$ 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 $\geq 25\,\text{kg/m}^2$ ($n = 10{,}689$) (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).

4. 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 (Haugen et al., 2011; Vikanes et al., 2010c; Kosus et al., 2016). 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 $< 25\,\text{kg/m}^2$ 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 $\geq 25\,\text{kg/m}^2$. 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 min of moderate to vigorous intensity physical activity per week, is causing many non-communicable diseases (Lee et al., 2012). 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 $25\,\text{kg/m}^2$ have higher levels of estrogen (Vikanes et al., 2010a), hypothesised to increase the risk of HG (Verberg et al., 2005). 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 (Jasienska et al., 2006). 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 (Koot et al., 2018). 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

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	1642 (6.1)	32 (1.9)	2.64 (1.74–4.01)	2.05 (1.33–3.16)
1–3 times per month	2765 (10.3)	38 (1.4)	1.85 (1.25–2.74)	1.53 (1.03–2.28)
1–2 times per week	6309 (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	5852 (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	1544 (14.4)	16 (1.0)	0.80 (0.45–1.41)	0.74 (0.42–1.31)
1–2 times per week	2982 (27.9)	39 (1.3)	1.01 (0.66–1.54)	1.01 (0.66–1.54)
3–5 times per week	3780 (35.4)	49 (1.3)	1 (reference)	1 (reference)
≥ 6 times per week	1428 (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.

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 (Nilsen et al., 2009). 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 (Vikanes et al., 2008). Previous research on HG in MoBa has shown that 74% of these women were hospitalised during their 1st trimester (Vikanes et al., 2010a). The large proportion of non-smokers in MoBa compared to the target population (Nilsen et al., 2009), 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 (Jenabi and Fereidooni, 2017).

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 (Brantsaeter et al., 2010). 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 (Kelly et al., 2014). 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 (Mudd et al., 2013). 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 = 61,827 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 was not specifically designed to study (Nilsen et al., 2009), 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.

5. 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.

Conflicts of interest

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

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Compliance with ethical standards.

Disclosure of interests.

All authors of this manuscript report no conflict of interest.

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