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The association of maternal adult weight trajectory with preeclampsia and gestational diabetes mellitus

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Abstract

Background—Preeclampsia (PE) and gestational diabetes mellitus (GDM) adversely affect pregnancy outcomes and the subsequent health of both mother and infant. It is known that elevated pre-pregnancy body mass index (BMI) is associated with increased risk of these obstetrical complications. However, little is known about the role of adult weight patterns prior to pregnancy.

Methods—Self-reported weight at ages prior to the current pregnancy was recorded in a prospective cohort study of 3567 pregnant women, allowing assessment of longitudinal pre-pregnancy weight trajectories and their association with subsequent PE and GDM in the study pregnancy.

Results—Women who would subsequently experience PE or GDM in the study pregnancy experienced on average almost double the rate of adult weight gain than other women (PE: additional 0.67 lbs/year, 95% confidence interval (CI): 0.20, 1.13 and GDM: additional 0.76 lbs/year, 95% CI: 0.46, 1.06). Women with mean adult annual weight gain above the 90th percentile (3.1 lbs/ year) had elevated risk of subsequent PE and GDM independent of their BMI at age 18 and of their obesity status at the time of the study pregnancy. Finite mixture trajectory modelling identified four monotonely ordered, increasing mean weight trajectories. Relative to the second lowest (most common) weight trajectory, women in the highest trajectory were at greater risk of PE (odds ratio [OR] 5.0, 95% confidence interval [CI] 2.9, 8.8) and GDM (OR 2.8, 95% CI 1.7, 4.5).

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Conclusions—These results indicate that higher adult weight gain trajectories prior to pregnancy may play a role in predisposing women to PE or GDM.

Keywords

preeclampsia; gestational diabetes mellitus; adult weight trajectory

Hypertensive disorders during pregnancy and gestational diabetes mellitus (GDM) adversely affect maternal, fetal and neonatal morbidity and mortality.¹⁻³ Women who experience these conditions during pregnancy are at increased risk for diabetes, hypertension and cardiovascular disease later in life.⁴⁻⁸ Similarly it has been shown that there are adverse sequelae for their offspring, including diabetes, obesity and intellectual performance.⁹⁻¹⁵ The association between pre-pregnancy weight or body mass index (BMI) and pregnancy outcome has been well established. Pre-pregnancy BMI has been shown among different populations to be associated with elevated risk of GDM and preeclampsia (PE) during pregnancy.¹⁶⁻²⁰ Furthermore, it has been suggested that higher maternal pre-pregnancy weight is associated with subsequent obesity and cardiovascular disease in the offspring.²¹⁻²²

Increased risk of PE has been shown in women who had higher adult weight gain²³⁻²⁴ and in women who had experienced weight cycling.²³ In a cohort of women aged 25-42 at enrolment, increased risk of GDM was shown to be associated with greater BMI at age 18 and greater weight gain between age 18 and enrolment.²⁵ To date, however, little attention has been paid to the impact on pregnancy outcome of the adult weight trajectory prior to pregnancy.

Chronic hypertension may play a mediating role in the relationship between weight gain and PE. A number of prospective cohort studies have shown increased risk of hypertension with increased adult weight gain.²⁶⁻²⁸

In summary, obesity at the time of pregnancy is associated with increased risk of hypertensive disorders and GDM in pregnancy. These conditions are in turn associated with poor infant and maternal health. Using a life course approach, we examined whether the nature of the adult longitudinal weight trajectory of women, prior to pregnancy, has impact on the incidence of PE and GDM.

Methods

Participants: The Omega Study

Participants were drawn from the Omega Study, a prospective cohort study of maternal dietary and other risk factors of PE and GDM. Women participating in the study attended prenatal care clinics affiliated with Swedish Medical Center, Seattle and Tacoma General Hospital, Tacoma, WA. Women eligible for inclusion were those who initiated prenatal care before 20 weeks' gestation, were at least 18 years of age, could speak and read English, planned to carry the pregnancy to term, and planned to deliver at either of the 2 study hospitals. Women with pre-gestational diabetes were excluded from the study.

Between December 1996 and February 2008, 5063 eligible women were approached and 4000 (79%) agreed to participate. Women were included in the study for only one pregnancy. We excluded 42 women with early pregnancy losses, 152 who were lost to follow-up and 239 that did not provide any self-reported weights. Hence, 3567 women remained, including 172 women diagnosed with chronic hypertension.

Enrolled participants were asked to take part in an hour-long interview in which trained research personnel used a structured questionnaire to elicit information regarding maternal sociodemographic and anthropometric characteristics (including self-reported height), lifestyle habits, and medical and reproductive histories. Self-reported weight prior to the study pregnancy at ages 18, 25, 30 and 35 years (where applicable, e.g., a woman aged 32 could report weight at ages 18, 25 and 30) was also recorded at the interview. Labour and delivery characteristics were ascertained by reviewing participants' hospital labour and delivery medical records and clinic records after delivery. The procedures used in this study were approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants provided written informed consent. Further details regarding the design, recruitment and patient characteristics can be found elsewhere.²⁹

Outcomes and covariates

Preeclampsia and chronic hypertension—The diagnosis of PE was made according to American College of Obstetricians and Gynecologists (ACOG) guidelines.³⁰ These guidelines defined PE as new onset hypertension with proteinuria in women who are beyond 20 weeks of gestation. Hypertension was defined as sustained blood pressure readings of 140/90 mmHg taken 6 hours apart. Proteinuria was defined as urine protein concentrations of 30 mg/dL on two or more random specimens collected at least 4 hours apart. Data on PE status was missing for 41 participants.

Chronic hypertension (CH) was determined on the basis of participants' report of a physician diagnosed condition. With a view to distinguishing adult weight trajectories in women who had CH by the time of the study pregnancy, we also considered a four-category variable, CHPE, including both CH and subsequent PE (neither, PE only, CH only, and PE and CH, the last group having CH with superimposed PE).

Gestational diabetes—The diagnosis of GDM was made as part of universal screening using the American Diabetes Association 2003 guidelines.³¹ All participants were screened at 26–28 weeks gestation using fasting and oral glucose load (50 g) screening tests. Women who had post-load glucose concentrations >140 mg/dl were then followed-up within 1–2 weeks with a three hour oral glucose (100 g) tolerance test. Women were diagnosed with GDM if two or more of the four diagnostic glucose concentration measurements exceeded the following: fasting > 95 mg/dl; 1 hour post-challenge >180 mg/dl; 2 hour post-challenge >155 mg/dl; 3 hour post-challenge >140 mg/dl. Data on GDM status was missing for 45 participants.

Other covariates—Potential confounders of the association between pregnancy outcome (PE/CHPE, GDM) and adult weight trajectory considered were education level (post high school vs. high school or less), parity (nulliparous vs. multiparous), maternal age (<25,

25-34, 35 years) and smoking history (never, former, current) at the time of the study pregnancy and whether the participant engaged in leisure time physical activity in the week before the interview (yes/no).

Statistical analysis

We estimated mean adult longitudinal weight trajectories where weight was regarded as the outcome in a linear model with age (and possibly age squared) and height as independent variables, with interaction between age and CHPE (GDM) status. Robust standard errors were calculated to accommodate the longitudinal records on individual subjects. This approach allows us to estimate the extent to which the average pre-pregnancy adult weight trajectory differs in those with and without subsequent CHPE (GDM).

We next considered *a priori* adult pre-pregnancy weight trajectory characteristics, without consideration of the pregnancy outcome, defined according to each woman's BMI at age 18 (the youngest age for which weight was recorded) and her average subsequent annual weight gain prior to the study pregnancy. Women were classified according to whether or not their BMI at age 18 was above the 90th percentile (24.0 kg/m²) and whether or not their subsequent average annual weight gain was greater than the 90th percentile (3.1 lbs/yr). The association of these trajectory characteristics with PE and GDM in the study pregnancy was assessed in logistic regression analysis. We also considered trajectories defined by annual average weight gain after age 18 and whether or not a woman was obese (BMI ≥ 30 kg/m²) at the time of the study pregnancy. These analyses excluded 152 women whose only weight record was at age 18.

Finally, finite mixture models were used to parametrically model mean adult weight trajectories for at most four weight trajectory groups with linear and quadratic terms for the trajectory over age, again without consideration of the pregnancy outcome.³²⁻³³ Because the distribution of weight was positively skewed, analyses were based on transformed weight (weight^{-1.5}) and then back-transformed. The approach is data-driven: models with 2-4 trajectories were considered and the model with the lowest value of the Bayesian Information Criterion was selected. The associated mean trajectories are determined by maximum likelihood. Each study participant was then assigned to the trajectory for which she had the highest probability of membership, given her observed weights.³² The association of trajectory membership with subsequent PE and GDM status in the study pregnancy was assessed in logistic regression models with PE (GDM) as the outcome.

The analyses of the association of weight trajectories with subsequent PE and GDM were repeated, including potential confounders. Analyses involving PE were carried out with and without 172 women who had CH. Sensitivity analyses were also considered for *a priori* weight trajectory groups defined according to 80th (rather than 90th) percentiles for BMI at age 18 and subsequent weight gain; restricting the cohort to nulliparous women only (where the influence on weight of previous pregnancies would not play a role); adjusting for maternal race; and for finite mixture models for trajectories for BMI, rather than weight.

The software packages Stata version 11 (StataCorp., College Station, TX) and SAS version 9.2 (SAS Institute, Inc., Cary, NC) were used in the analyses.

Results

Table 1 summarizes characteristics of the cohort at the time of the study pregnancy, overall and for those with PE and GDM. Between age 18 and the study pregnancy, women who would experience PE gained, on average, 44.0 lbs (standard deviation (SD) 39.1 lbs), or 3.4 lbs/year, and women who would experience GDM gained, on average, 33.9 lbs (SD 34.8 lbs), or 2.4 lbs/year. Figure 1 summarizes weight (lbs) at 18, 25, 30 and 35 years, overall, and for those with PE and GDM. Median and interquartile ranges for weights of women who would subsequently experience PE in pregnancy were higher than the rest of the cohort at all ages, whereas for women who would develop GDM they were higher at older ages.

Adult pre-pregnancy mean weight trajectories by subsequent CHPE/GDM status

Linear models were fitted for weight as outcome and with age, CHPE (GDM) and their interactions as primary independent variables, adjusting for height. Quadratic coefficients in age were not statistically significant. Figure 2 illustrates estimated mean weight trajectories from age 18 by outcome of the study pregnancy for women of height 1.65m.

Data on PE during the study pregnancy was available for 3526 women. Of these, 3.7% (n=129) experienced CH only, 2.2% (n=79) PE only and 1.1% (n=39) experienced both CH and PE. Women who would experience PE, but not CH, had similar mean weight at age 18 as women who would experience neither condition, whereas women who would experience CH were on average heavier at age 18. At age 18 women who would experience CH only were on average 9.6 lbs (95% CI 6.2, 12.9) heavier and women who would experience PE and CH were on average 13.5 lbs (95% CI 7.4, 19.6) heavier than women who would experience neither condition. Women who would experience neither PE nor CH had mean annual weight increase after age 18 of 0.81 lbs/yr (95% CI 0.74, 0.88). Mean annual weight change in women with PE but not CH was 0.67 lbs yr (95% CI 0.20, 1.13) greater than that for women with neither condition and for women with CH but not PE 0.62 lbs/yr (95% CI 0.26, 0.98) greater. Women who would experience both CH and PE had a mean annual increase in weight prior to the study pregnancy that was 2.31 lbs/yr (95% CI 1.64, 2.99) greater than that in women who would experience neither condition. Analysis restricted to women without CH yielded very similar estimates for PE only.

There was no significant difference in mean weight at age 18 in women who would and would not subsequently experience GDM in the study pregnancy. However, average annual weight change after age 18 in women who would experience GDM was 0.76 lbs/yr (95% CI 0.46, 1.06) greater than the average annual weight gain in women who would not (0.82 lbs/yr, 95% CI 0.75, 0.90).

A priori defined weight trajectory groups

We next considered *a priori* defined weight trajectory characteristics, first classifying women according to their BMI at age 18 (relative to 24.0 kg/m², the 90th percentile) and their mean annual weight gain thereafter (relative to 3.1 lbs/year, the 90th percentile). Here we are considering adult pre-pregnancy weight trajectories “anchored” by BMI at age 18. Records for 3374 women were available for this analysis, which excluded women under age

25 at the time of the study pregnancy who consequently did not have information on weight gain after age 18. Table 2 shows the associations with PE and GDM. Those with higher rate of weight gain prior to the study pregnancy were at greater risk of PE and GDM, independent of their weight at age 18, again indicating that adult weight gain may be associated with PE and GDM. There was no indication of effect modification of the association of adult weight gain with PE and GDM by BMI at age 18 (data not shown).

In secondary analyses, we categorized women according to BMI at age 18 and whether or not they *lost* weight between age 18 and the study pregnancy. Independent of BMI at age 18, in adjusted analyses, compared to women who lost weight (14.0% of women), women who gained weight were at greater risk of PE (OR 11.1, 95% CI 2.7, 45.5) and of GDM (OR 3.1, 95% CI 1.6, 5.9). Exploratory nonparametric smoothing indicated that risk of both outcomes increased monotonely as weight gain between age 18 and the study pregnancy increased (data not shown).

We also considered weight trajectory groups anchored at the study pregnancy, classifying women according to their obesity status (BMI ≥ 30 kg/m²) at the time of the study pregnancy and their mean annual weight gain from age 18 (relative to 3.1 lbs/year, the 90th percentile). Table 2 shows that higher weight gain prior to the study pregnancy is a risk factor for PE and GDM, independent of obesity status at the time of conception. There was no indication of effect modification of the association of adult weight gain with PE and GDM by obesity at the time of study pregnancy (data not shown). Results were similar when BMI at age 18 was included (data not shown).

Sensitivity analyses including only nulliparous women and based on 80th (rather than 90th) percentile cutoffs for BMI at age 18 and subsequent weight gain and analyses adjusting for maternal race yielded similar results for PE and GDM.

Modelling adult pre-pregnancy weight trajectory groups

In finite mixture trajectory modeling we assume that, rather than there being a single common mean trajectory, different members of the population may be associated with different mean trajectories, which may be partitioned into groups.³²⁻³³ The four fitted weight trajectories (solid lines) are shown in Figure 3. Figure 3 also shows, for each trajectory, observed pre-pregnancy weight paths (dashed lines) of three study women assigned to that trajectory group (women whose median weight was at the 25th, 50th and 75th percentile for that group). 12.8% of study participants were assigned to trajectory group 1, 46.3% to trajectory group 2, 32.0% to group 3 and 8.9% to group 4. The estimated mean trajectories are all monotone increasing and do not intersect (Fig 3). Trajectory 4, with the highest mean weight at age 18, is also the trajectory with the highest mean weight at age 35. The monotone ordering of the mean trajectory paths means that women on the highest weight trajectory will also likely be those with highest pre-pregnancy weight.

These adult weight trajectories were identified without consideration of the status of the subsequent study pregnancy. The association between trajectory group and PE/GDM status is shown in Table 3, with trajectory group 2 as the reference. Women in the two highest trajectory groups were at significantly greater risk of PE. When women who were diagnosed

with CH prior to the study pregnancy were excluded, the association of trajectory group with PE remained but was attenuated. (Of women with CH, 3.5% were in group 1, 29.6% in group 2, 37.8% in group 3 and 29.1% in group 4.) The odds of GDM were significantly higher in trajectory group 4 (highest weight trajectory).

Sensitivity analyses including only nulliparous women and adjusting for maternal race yielded similar results for PE and GDM. Analyses considering group-based trajectories for BMI, rather than weight, showed similar associations of increasing trajectory with increased PE and GDM risk (data not shown).

Comment

We considered three approaches for assessing the role of adult pre-pregnancy weight trajectory on pregnancy outcome. First, we assessed whether adult weight trajectory differed according to subsequent pregnancy outcome. Women who would subsequently experience PE or GDM in the study pregnancy experienced on average almost double the rate of adult weight gain compared to other women. We then considered characterising adult weight trajectories (either *a priori* or by finite mixture modelling) independent of study pregnancy outcome, and assessing whether those trajectory groups were differentially associated with risk of PE or GDM. Women with mean annual weight gain (from age 18 until the study pregnancy) above the 90th percentile had elevated risk of subsequent PE and GDM relative to other women, independent of their BMI at age 18 and independent of their obesity status at the time of the study pregnancy. Finite mixture longitudinal trajectory modeling identified four monotonely ordered, increasing mean weight trajectories. Relative to the second lowest (most common) weight trajectory, women in the highest trajectory were at elevated risk of subsequent PE and GDM.

These analyses, while consistent with the body of work that indicates that elevated pre-pregnancy weight is associated with increased risk of PE and GDM, add to that knowledge in a number of ways. Women who would experience PE (without CH) or GDM were, on average, of comparable weight at age 18 to those who would not experience these conditions. Women with CH before the study pregnancy were, on average, 12 lbs heavier at age 18. Women who would experience PE/CH or GDM gained weight at a more rapid rate than other women after age 18 and this was particularly the case for women who would experience both PE and CH.

When mean weight trajectories are parametrically modeled without consideration of subsequent pregnancy outcome, the higher mean weight trajectories are also those with the higher mean pre-pregnancy weight. Hence it is not clear whether the associated increased risk of PE and GDM reflects the trajectory path itself or the correspondingly high pre-pregnancy weight. The analyses which consider *a priori* weight trajectory characteristics throw light on this question as women who have had higher rate of weight gain after age 18 are at greater risk for PE and GDM, independent of their BMI at age 18 and independent of obesity status at the time of the study pregnancy. This is consistent with the observation by Frederick and colleagues,²³ using earlier enrollment for this cohort, that, adjusting for weight at age 18, women who gained more than 10kg between age 18 and the study

pregnancy were at greater risk for PE. Our results are also consistent with the observation that weight gain after age 18 is associated with GDM.²⁵ Hence, these analyses indicate that adult weight trajectory plays a role in predisposing a woman to PE or GDM, rather than just the endpoint of that trajectory, the pre-pregnancy weight.

Change in pre-pregnancy BMI from first to second pregnancy has been shown to be associated with increased risk of PE and GDM as well as other adverse pregnancy conditions.³⁴ We are aware of few other published reports assessing the association between maternal adult weight trajectory during the reproductive years and the risk of PE or GDM. Our results are consistent, however, with a relatively large body of literature that documents adverse health outcomes associated with adult weight gain in non-pregnant women and men.³⁵⁻³⁹

Several limitations of the present study merit discussion. The cohort consisted primarily of white, well-educated women from the U.S. Pacific Northwest and the generalizability of results may therefore be limited, although adjustment for maternal race in sensitivity analyses did not alter our findings. Errors in reporting of weights may be present. However, self-reported weights in other studies have been shown to be valid.⁴⁰ Although we adjusted for several known and suspected confounders, we cannot exclude the possibility of residual confounding. Factors such as diet, physical activity and mental health during the adult pre-pregnancy years were not recorded in our study and information on previous pregnancy outcomes was self-reported and not regarded as being of sufficient reliability to include. Physical activity *during* pregnancy was recorded and may be regarded as a proxy for typical adult pre-pregnancy physical activity. We adjust for physical activity during pregnancy, which may be in the causal pathway between weight trajectory and pregnancy outcome. However, the impact of this adjustment was modest. In future studies of the role of adult weight trajectory, measures of these potential confounders would be valuable. Younger women enrolled in this study will contribute shorter adult weight records. This would be a source of bias if the weight records of the older women in the study do not reflect what the younger women's weights would be when they reached those ages. We attempt to address this by adjusting for parity in our primary analysis and by excluding multiparous women in sensitivity analyses, but cannot account for temporal changes in weight trajectories. Finally, some of these results are data-driven and hence must be regarded as hypothesis-generating.

Our findings are biologically plausible. While we are not aware of experimental studies linking adult weight gain to insulin resistance and blood pressure control in pregnancy, it is clear that adult weight gain will impact physiological functions which, in turn, may plausibly impact the risk of PE or GDM via several biologic pathways. If these findings are independently replicated, greater clarity regarding biological pathways may emerge. These results support targeting of young women towards healthful behavioral changes that lead to weight control during their reproductive years.

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Figure 1.
Weight distribution (logarithmic scale) by age

Figure 2.
Estimated mean adult weight trajectory by pregnancy outcome (height 1.65m)

Figure 3.

Estimated mean adult weight trajectory groups and observed weight paths for women whose median weight is at the 25th, 50th and 75th percentile for each group

Table 1

Characteristics of the Omega Cohort at the Time of Study Pregnancy

	All women (n=3567)	Preeclampsia (n=118)	GDM (n=186)
Continuous variables (Mean (SD))			
Maternal Age	32.7 (4.4)	32.9 (5.4)	34.0 (4.7)
Pre-pregnancy BMI (kg/m ²)	23.6 (4.9)	28.8 (8.3)	26.7 (7.1)
Height (m)	1.67 (.07)	1.67 (.07)	1.64 (.08)
Change in weight from age 18 (lbs)	17.9 (23.4)	44.0 (39.1)	33.9 (34.8)
Categorical variables (n (%))^a			
Married	3260 (91.4)	102 (86.4)	167 (89.8)
Post high school education	3433 (96.2)	107 (90.7)	176 (94.6)
Race			
White	3075 (86.3)	101 (85.6)	135 (72.6)
African American	64 (1.8)	4 (3.4)	2 (1.1)
Asian	256 (7.2)	5 (4.2)	35 (18.8)
Other	169 (4.7)	8 (6.8)	14 (7.5)
Nulliparous	2246 (63.0)	82 (69.5)	110 (59.1)
Physically active in week before interview	2868 (80.4)	90 (76.9)	139 (75.1)
Smoking history			
Never	2549 (71.7)	90 (76.9)	138 (74.6)
Former	789 (22.2)	20 (1.1)	31 (16.8)
Current	218 (6.1)	7 (6.0)	16 (8.6)
Alcohol consumption in pregnancy			
No	2443 (69.5)	94 (82.5)	139 (75.5)
Yes	351 (10.0)	8 (7.0)	19 (10.3)
Stopped during pregnancy	722 (20.5)	12 (10.5)	26 (14.1)

^a Numbers do not add to column total because of missing observations for maternal race (3 missing), physical activity (1 missing), smoking history (11 missing), alcohol consumption (41 missing).

Table 2
Adjusted^a Odds Ratios for Preeclampsia and Gestational Diabetes Mellitus, Comparing *a priori* Weight Trajectory Groups

	Preeclampsia			Gestational Diabetes		
	All women		Excluding chronic hypertension	All women		
	OR	95% CI	OR	95% CI	OR	95% CI
Trajectory anchored by BMI at age 18						
Heavy at age 18 ^b	1.5	[0.9, 2.7]	0.9	[0.4, 2.1]	1.0	[0.6, 1.7]
Weight gainer ^c after age 18	4.7	[3.0, 7.4]	3.3	[1.8, 6.1]	3.0	[2.0, 4.5]
Trajectory anchored by obesity status at study pregnancy						
Weight gainer ^c after age 18	2.1	[1.1, 3.7]	1.8	[0.8, 4.0]	1.9	[1.1, 3.1]
Obese ^d pre-pregnancy	4.5	[2.5, 7.9]	2.8	[1.3, 6.1]	2.2	[1.3, 3.7]

^a Adjusted for height, parity, maternal age, smoking, education and leisure time physical activity

^b Heavy at age 18 defined as BMI above the 90th percentile (24.0 kg/m²)

^c Weight gainer defined as average annual weight gain above the 90th percentile (3.1 lbs/yr)

^d BMI ≥ 30 kg/m²

Table 3
Adjusted^a Odds Ratios for Preeclampsia and Gestational Diabetes Mellitus, Comparing Modeled Weight Trajectory Groups

Weight trajectory ^b	Preeclampsia				Gestational Diabetes			
	All women		Excluding chronic hypertension		All women			
	n	OR	95% CI	n	OR	95% CI	n	OR
Group 1	450	1.1	[0.5, 2.2]	444	1.0	[0.5, 2.2]	454	1.2
Group 2	1632	Reference		1583	Reference		1639	Reference
Group 3	1130	2.5	[1.5, 4.0]	1066	1.8	[1.1, 3.1]	1125	1.2
Group 4	314	5.0	[2.9, 8.8]	265	2.5	[1.2, 5.3]	304	2.8

^a Adjusted for height, parity, maternal age, smoking, education and leisure time physical activity.

^b Weight trajectory groups are ordered from lowest (1) to highest (4)