Published in final edited form as:
Obesity (Silver Spring). 2010 November ; 18(11): 2184–2190. doi:10.1038/oby.2010.25.

The impact of exposure misclassification on associations between prepregnancy body mass index and adverse pregnancy outcomes

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Abstract

Prepregnancy body mass index (BMI) is a widely used marker of maternal nutritional status that relies on maternal self-report of prepregnancy weight and height. Pregravid BMI has been associated with adverse health outcomes for the mother and infant, but the impact of BMI misclassification on measures of effect has not been quantified. The authors applied published probabilistic bias analysis methods to quantify the impact of exposure misclassification bias on well-established associations between self-reported prepregnancy BMI category and five pregnancy outcomes (small- and large-for gestational age birth (SGA; LGA), spontaneous preterm birth (sPTB), gestational diabetes (GDM), and preeclampsia) derived from a hospital-based delivery database in Pittsburgh, PA (2003-2005; n=18 362). The bias analysis method recreates the data that would have been observed had BMI been correctly classified, assuming given classification parameters. The point estimates derived from the bias analysis account for random error as well as systematic error caused by exposure misclassification bias and additional uncertainty contributed by classification errors. In conventional multivariable logistic regression models, underweight women were at increased risk of SGA and sPTB, and reduced risk of LGA, while overweight, obese, and severely obese women had elevated risks of LGA, GDM, and preeclampsia compared with normal-weight women. After applying the probabilistic bias analysis method, adjusted point estimates were attenuated, indicating the conventional estimates were biased away from the null. However, the majority of relations remained readily apparent. This analysis suggests that in this population, associations between self-reported prepregnancy BMI and pregnancy outcomes are slightly overestimated.

Keywords

pregnancy; body mass index; epidemiology; birth weight

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INTRODUCTION

Prepregnancy body mass index (BMI) is a marker of maternal nutritional status that is often ascertained by recalled weight and height. Researchers and clinicians rely on self-reported prepregnancy weight because most women do not have a preconception visit where weight is measured. Height may be self-reported as well because it saves time in clinical and research settings. The concern with a self-reported weight and height is the amount of misreporting. On average, women underreport their weight by approximately 1 to 3 kg (1-7), but greater amounts of underreporting as well as overreporting also occur (1-3,8). While most women recall their height within 1 inch of their measured height, greater deviations are common (1-3,7). Therefore, misreporting of both weight and height leads to measurement error in the calculation of prepregnancy BMI and classification of women into BMI categories (7-9).

Misclassification of prepregnancy BMI category can lead to bias in epidemiologic studies. This bias is important to understand because maternal prepregnancy BMI is a widely studied exposure that has been associated with numerous negative health consequences for mothers and infants, including ovulatory infertility, miscarriage, gestational diabetes mellitus (GDM), preeclampsia, cesarean delivery, congenital malformations, small- and large-for-gestational age birth (SGA, LGA), spontaneous preterm birth (sPTB), maternal and infant mortality, childhood obesity, and later-life childhood outcomes (10-13). Although investigators often include a few lines in their manuscripts acknowledging the potential limitation of misreporting of weight and height, they do not formally quantify the bias. Instead, authors frequently state that because the misclassification of BMI is unlikely to vary by outcome (i.e., it is nondifferential), their results are biased towards the null and therefore underestimate the true effect (e.g., (14-19)). This interpretation is incorrect even if the bias is towards the null (20, 21). Moreover, several conditions must be met to ensure bias towards the null, including requiring a binary exposure variable (21-23). The direction of bias cannot be assumed when the exposure variable is polytomous (22). as is typically the case with BMI classification. Without quantifying the bias due to misclassification, conventional effect estimates may mislead readers, by giving them exaggerated confidence in the precision of the results and/or by leading them to incorrect conclusions about the strength and/or direction of the association.

The objective of this study was to apply published probabilistic bias analysis methods developed by Lash and Fox (24,25) to formally quantify the impact of exposure misclassification bias on well-established associations between prepregnancy BMI and five pregnancy outcomes: SGA, LGA, sPTB, GDM and preeclampsia.

METHODS AND PROCEDURES

Data came from the Magee Obstetric Medical and Infant (MOMI) Database. The MOMI Database, established in 1995, routinely collects comprehensive maternal, fetal, and neonatal outcomes from electronic and medical record data on all women delivering at Magee-Womens Hospital in Pittsburgh, Pennsylvania (26). The database is surveyed periodically to maintain its accuracy by direct comparison at random with patient charts, and also by examining frequencies for variables that contain data outliers upon download, which once identified were verified or corrected by means of medical chart review. Personal identifying information in the database was eliminated to ensure confidentiality. The Institutional Review Board approved this study.

There were 22,442 deliveries of singleton, live-born infants without congenital anomalies from 20 to 42 weeks gestation at Magee-Womens Hospital from January 1, 2003 to December 31, 2005. We excluded deliveries with missing data on infant birth weight (n=41), maternal height (n=257), prepregnancy weight (n=1,299), or one of the covariates in the final model (n=1,307).

We also eliminated 1,176 observations that represented a second or third delivery from the same woman in the dataset. The final analytical sample was 18,362 births. There were no meaningful differences in maternal race/ethnicity, education, or age between the cohort of available deliveries and the final analytical sample (data not shown).

Prepregnancy weight was abstracted from the prenatal flow sheet, where maternal self-report of prepregnancy weight is noted at the first prenatal visit. Recalled height was abstracted from the Mother's Worksheet, a form completed by women at delivery for the birth record. Prepregnancy BMI [weight (kg) / height $(m)^2$] was categorized using the cut-points proposed by the World Health Organization:(27) underweight (<18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), obese (30 to 34.9 kg/m^2) and severely obese (≥35 kg/m^2).

Gestational age was ascertained from the birth attendant's final estimate of gestational length based on all available perinatal factors and assessments, including ultrasound reports. Although the database did not indicate how gestational age was specifically determined in each patient, 78% of patients that deliver in our hospital have a dating ultrasound by 20 weeks gestation (Magee-Womens Hospital quality assurance data, 2006). SGA and LGA were defined as live born infants that were <10th percentile or >90th percentile, respectively, of birth weight according to nomograms based on race, gender and gestational age from a U.S. reference population (28). Spontaneous preterm birth was defined as a delivery occurring at 20 to less than 37 completed weeks gestation after preterm labor with intact membranes or preterm prelabor rupture of the fetal membranes. International Classification of Diseases, Ninth Edition codes were used to diagnose GDM (648.8×) and preeclampsia (mild preeclampsia (642.4×), severe preeclampsia (642.5×), or eclampsia (642.6×)) (29).

Statistical analysis

Conventional analysis—First, we used multivariable logistic regression models to generate conventional odds ratios and 95% confidence intervals for the associations between prepregnancy BMI and each pregnancy outcome. Indicator variables for BMI categories with normal weight as the referent were used in the models. Models were adjusted for potential confounders identified a priori: maternal race/ethnicity, age, parity, marital status, education, smoking status, clinic/private patient, and year of delivery.

Sensitivity analysis—We then used published probabilistic bias analysis methods (24,25) to assess the bias and uncertainty caused by errors in the classification of prepregnancy BMI category. The methods rely on Monte Carlo simulation to modify the existing data set to the data that would have been observed had the misclassified variable been correctly classified, assuming given classification parameters. The general approach to these simulations is provided by Fox et al. (25), with the extension to polytomous variables described in detail by Lash et al. (24). Briefly, we used the validation data described below to inform estimates of the positive predictive value for each BMI category. We assumed nondifferential misclassification of BMI category because a woman's report of prepregnancy weight and height at the first prenatal visit cannot be influenced by a late-pregnancy or delivery outcome. We parameterized a binomial distribution for the predictive values, and then conducted a Bernoulli trial for every observation in the dataset. For each trial, the probability of success was set equal to the predictive value for the BMI category of the observation. For example, for a overweight woman, the probability of success in her Bernoulli trial was equal to 76%. When trials returned with a result of “true,” we did not change the BMI category value assigned to the woman. When trials returned a finding of “false,” the original BMI category value was changed to the new value based on the predictive values from the validation study. For instance, a woman originally classified as overweight whose Bernoulli trial returned a finding of “false” would have 33%,

63%, and 4% probabilities of being reclassified to normal weight, obese, and severely obese, respectively. This method did not account for other maternal characteristics or the self-reported BMI value in predicting the reassigned BMI category.

We then re-estimated multivariable logistic regression models using the modified dataset to calculate estimates of association that were not only adjusted for the aforementioned confounders, but also accounted for the simulated misclassification errors in BMI category. These steps were repeated for 100,000 iterations to obtain 2 sets of sensitivity analysis point estimates and 95% simulation intervals: (1) estimates that reflect adjustment for the exposure misclassification bias and additional uncertainty contributed by classification errors (i.e., systematic error only); and (2) estimates that account for this misclassification bias as well as random error. (30)

Validation data—Fox et al. (25) recommend using an external validation study to assign distributions of the classification parameters used in the sensitivity analysis program when internal validation data are not available. In this retrospective cohort, we did not have internal validation study available. Therefore, we used data from the 1999-2006 National Health and Nutrition Examination Survey (NHANES), a nationally-representative survey designed to assess the health and nutritional status of non-institutionalized Americans (31). In a large subsample, NHANES collected interview-based self-reported weight and height as well as measured weight and height. We limited this subsample with self-reported and measured weight and height to nonpregnant women of childbearing age (16-49 years; n=5,577).

For each woman, we calculated a measured BMI and a BMI based on self-report, and classified women into self-reported and measured BMI categories. Then, we calculated the predictive values as the probability that women in each self-reported BMI category were truly underweight, truly normal weight, truly overweight, truly obese, and truly severely obese. To obtain the predictive values, we weighted the NHANES data to account for the complex sampling design.

RESULTS

Women who delivered live-born, nonanomalous infants at Magee-Womens Hospital from 2003-2005 tended to be normal weight, white, 30 years or older, college-educated, married, multiparous, and non-smokers (Table 1). Almost 10% were obese and 7% were severely obese.

In the conventional analysis adjusting for maternal race, age, marital status, education, parity, smoking, clinic/private patient status, and delivery year, underweight women were at increased risk of SGA and sPTB, and reduced risk of LGA compared with normal weight women (Table 2). Overweight, obese, and severely obese women had elevated risks of LGA, GDM, and preeclampsia compared with normal-weight women, with a tendency for the conventional odds ratio to increase with rising self-reported BMI category.

Table 3 displays the NHANES validation data used to estimate errors in self-reported BMI category. Self-reported BMI category misclassified 6.8% to 28.1% of reproductive-aged women. The percent of women whose self-reported and measured BMI category agreed was highest among normal-weight (85.3%) and severely obese (93.1%) women, and was lowest among underweight (76.4%), overweight (75.7%), and obese (71.9%) women. Self-reported BMI category was underestimated as well as overestimated. For example, among women whose self-reported height and weight classified them as overweight, 7.6% were truly normal weight, 15.3% were truly obese, and 1.4% were truly severely obese based on measured weight and height. These data were used to inform the classification parameters in the bias analysis.

Application of the probabilistic bias analysis methods to account for the non-differential misclassification of BMI category suggested that the conventional odds ratios relating BMI to the adverse pregnancy outcomes were biased away from the null (Table 2). For every association studied, the bias analysis adjusted point estimates, which accounted for the BMI misclassification bias and additional uncertainty contributed by classification errors, were attenuated compared with the conventional odds ratios. Moreover, accounting for both systematic error and random error in the total error results led to wider intervals around the point estimates.

For example, the adjusted odds ratio for sPTB among underweight women in the conventional analysis [adjusted odds ratio 1.44 (95% confidence interval (CI): 1.11, 1.86)] was attenuated to a point estimate of 1.28 (95% simulation interval: 1.05, 1.52) after accounting for systematic error only (bias analysis result). After taking into account systematic and random error, the point estimate (95% simulation interval) was 1.28 (0.93, 1.74).

Despite the attenuation of the estimates, the dose-dependent associations relating prepregnancy overweight, obesity, and severe obesity to LGA, GDM, and preeclampsia remained readily apparent. For instance, in the conventional models the GDM adjusted odds ratio (95% CI) were 2.56 (2.10, 3.11), 5.18 (4.18, 6.53), and 8.02 (6.43, 10.01) for overweight, obese, and severely obese women, respectively, compared with normal-weight women. The estimates for these groups weakened somewhat to 2.09 (1.63, 2.67), 3.97 (3.06, 5.11), 5.80 (5.26, 7.31), respectively after accounting for random error and systematic error caused by misclassification of BMI category.

After adjusting for misclassification of BMI category and random error, the elevated risk of SGA and sPTB among underweight women weakened and included unity.

DISCUSSION

Self-reported prepregnancy BMI is an indicator of maternal nutritional status that is widely used in clinical and research settings and for population-based surveillance. While it is well known that BMI is often misreported (2,3), the effect of this error on measures of association has received little attention. Because prepregnancy BMI is one of the strongest modifiable risk factors for poor pregnancy outcomes (10-13), quantifying the impact of the bias is critical.

In this large cohort of women delivering live-born infants in Pittsburgh, we observed expected associations between prepregnancy BMI category and five pregnancy outcomes, both in terms of direction and magnitude of effect, when using conventional analytic techniques. After applying probabilistic bias analysis methods that accounted for error caused by misclassification of BMI, the adjusted point estimates were attenuated, suggesting that the conventional results were biased away from the null. However, the dose-response risk of LGA, GDM, and preeclampsia in overweight, obese, and severely obese women remained apparent. The significant effect of maternal prepregnancy underweight on risk of SGA and sPTB weakened and was no longer statistically significant.

Our results indicating that the weight and height reporting error biases results away from the null is in direct contradiction to the common assumption of bias towards the null with nondifferential misclassification of BMI. Indeed, investigators frequently point out data showing that women tend to underreport their weight and overreport their height, and that the underreporting of weight becomes more exaggerated as BMI increases (1-3,5). Researchers therefore conclude that BMI category is underestimated, and the results are biased towards the null (e.g., (14-19)). However, many conditions must be met to ensure bias towards the null, including a binary exposure variable; misclassification probabilities that are exactly nondifferential; independence of misclassification from other variables in the analysis, and

absence of interaction between misclassification and other sources of systematic error (21-23). Clearly, in studies of polytomous self-reported BMI categories, bias towards the null cannot be assumed. Schieve et al. conducted a study validating self-reported versus measured pregnancy delivery weight in the 1988 National Maternal and Infant Health Survey (32). When comparing the effect of self-reported versus measured gestational weight gain category on the risk of low and high birth weight, they observed bias towards the null for certain levels of gestational weight gain, and away from the null for others. In the large nationally-representative sample of childbearing-aged U.S. women that served as the validation data for our study, we observed that both underreporting and overreporting of recalled BMI were prevalent and meaningfully differed by BMI category. Obviously, in this situation, formal bias analysis is the only reliable way to estimate the direction and magnitude of the misclassification bias.

Our validation study using reproductive-aged women in NHANES illustrated a moderate degree of misclassification in BMI category. Interestingly, while absolute error in measured versus self-reported weight may rise with increasing BMI, (1-3,8) we observed the greatest amount of agreement between measured and self-reported BMI among severely obese women. Without an upper bound on this BMI category, women may be further from the classification cut-point of 35 kg/m^2, and therefore misreporting is less likely to move them into a lower BMI category. The validity of this BMI category is important given that severely obese women are the fastest growing segment of the population (33). Other investigators have used NHANES data to cross-classify reported and measured BMI category, but categorized BMI differently, did not restrict the sample to reproductive-aged women and/or used fewer waves of data (7, 34). To obtain the most accurate classification parameters for the bias analysis, we felt that it was important to replicate these studies with a sample most suitable for our objective.

Nevertheless, our use of NHANES for the validation study data had limitations. Using the predicted probabilities generated from NHANES assumes that the misclassification of BMI category was the same in this sample as in our cohort. This may not be the case, given that NHANES data were from a nationally-representative sample of childbearing-aged women with height and weight self-reported and measured on the same day, and ours was a convenience sample of pregnant women recalling their height and weight from several weeks in the past, after gestational weight gain has started to occur. The ideal validation study would have been one that was a random subsample of our current cohort, where women's weight was measured before pregnancy and then recalled at the first prenatal visit. We did not have these data available, and we were unaware of published papers that reported appropriate data in pregnant women or publically-available datasets from a pregnant cohort. Because investigators have drawn similar conclusions about weight-related measurement error in pregnant and nonpregnant women (4,6), we felt that the use of NHANES validation data were reasonable. However, this is an important area that requires additional study. Investigators designing prospective research studies should consider incorporating an internal validation study to help correct with errors in the analysis.

Our bias analysis was limited in its consideration of exposure misclassification only. However, misclassification is thought to be a much greater concern in epidemiologic research than unmeasured confounding, for instance (35). Additionally, accuracy of weight and height reporting varies by numerous individual-level factors such as education and age (1-3,8,34) and may also depend on the BMI value within each category. Our probabilistic bias analysis did not account for differential classification by these characteristics. We assumed nondifferential misclassification, but scenarios in which differential misclassification may apply are also possible, such as misreporting of weight and height differing for multiparous women with a previous adverse outcome compared with women without a previous adverse outcome. One may incorporate varying scenarios as a sensitivity analysis for the bias analysis. We will provide the SAS code to interested users upon request. We were unable to explore potential

linear or curvilinear relations between BMI and the logit of pregnancy outcomes because probabilistic bias analysis methods require categorized variables. We also did not consider modifying effects of gestational weight gain on BMI-adverse outcome associations. Nevertheless, it is a research priority to additionally study how misclassification of variables that rely on self-reported prepregnancy weight and/or height, such as gestational weight gain adequacy and postpartum weight retention, are impacted by this bias.

Our analysis suggests that in this population of pregnant women in Pittsburgh, associations between self-reported prepregnancy BMI and adverse birth outcomes are slightly overestimated due to exposure misclassification. However, this bias did not substantially alter the conclusions drawn. In the bias analysis estimates, it was still clear that the higher the BMI, the greater the risk of several complications. Our results underscore the importance of maternal prepregnancy overweight and obesity for poor pregnancy outcomes. Given the world-wide obesity epidemic, the application of this methodology to additional pregnancy outcomes and health outcomes outside of pregnancy is an important area for continued work.

To our knowledge, we are the first to apply bias analysis methods to quantify the influence of the widely documented measurement error in BMI category on adverse health outcomes. These methods are relatively easy to implement, and can account for misclassification of binary or polytomous exposures, outcomes, and/or covariates. We conclude that probabilistic bias analysis is a relatively straightforward analytic technique that epidemiologists in any substantive area of research will find useful when misclassification is a concern.

Acknowledgments

Funding Source: This work was supported by the National Institutes of Health [HD056999 to L.M.B., MH074092 to L.M.B.]

The authors thank Dr. Timothy Lash of Boston University for providing them with the SAS code needed to perform this analysis, and for his advice concerning many aspects of this project. This project would not have been possible without his generous support.

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Table 1

Characteristics of Deliveries in the Magee Obstetric Medical and Infant Database (n=18,362).

	Percent
Maternal Characteristics	
Prepregnancy body mass index, kg/m^2	
Underweight (<18.5)	4.6
Normal weight (18.5 to 24.9)	57.3
Overweight (25.0 to 29.9)	21.6
Obese (30.0 to 34.9)	9.7
Severely obese (≥35.0)	6.7
Maternal race/ethnicity	
White	77.3
Black	18.0
Other	4.7
Maternal age, years	
<20	6.2
20-29	41.4
≥30	52.5
Maternal education	
Less than high school	8.5
High school or equivalent	21.6
Some college	23.2
College graduate	46.7
Marital status	
Unmarried	34.2
Married	65.8
Parity	
0	45.7
≥1	54.3
Smoking status	
Smokers	14.5
Non-smokers	85.5
Outcomes	
Gestational diabetes mellitus	4.2
Preeclampsia	5.3
Small-for-gestational age birth	8.4
Large-for-gestational age birth	9.7
Spontaneous preterm birth <37 weeks	5.9

Obesity (Silver Spring). Author manuscript; available in PMC 2011 November 1.

Table 2

Conventional Results and Bias Analysis Estimates and 95 Percent Simulation Intervals for Selected Outcomes (n=18,362).

	Conventional result [a]		Bias analysis result [b]		Total error result [c]	
	Adjusted [d] odds ratio	95% confidence interval	Adjusted [d] point estimate	95% simulation interval	Adjusted [d] point estimate	95% simulation interval
SGA						
Underweight [e]	1.46	1.18, 1.81	1.30	1.11, 1.50	1.30	1.00, 1.67
Normal weight	1.00	referent	1.00	referent	1.00	referent
Overweight	0.87	0.76, 1.00	0.90	0.81, 0.99	0.89	0.76, 1.06
Obese	0.98	0.82, 1.18	0.94	0.83, 1.05	0.94	0.76, 1.16
Severely obese	0.80	0.64, 1.01	0.85	0.76, 0.95	0.85	0.68, 1.06
LGA						
Underweight	0.49	0.34, 0.71	0.68	0.52, 0.85	0.68	0.45, 0.98
Normal weight	1.00	referent	1.00	referent	1.00	referent
Overweight	1.57	1.40, 1.78	1.41	1.30, 1.54	1.41	1.22, 1.64
Obese	1.77	1.51, 2.08	1.69	1.52, 1.86	1.69	1.40, 2.03
Severely obese	2.12	1.77, 2.54	1.88	1.73, 2.04	1.88	1.73, 2.24
sPTB						
Underweight	1.44	1.11, 1.86	1.28	1.05, 1.52	1.28	0.93, 1.74
Normal weight	1.00	referent	1.00	referent	1.00	referent
Overweight	1.00	0.85, 1.17	0.99	0.88, 1.11	0.99	0.81, 1.20
Obese	1.01	0.81, 1.25	0.99	0.86, 1.14	1.00	0.76, 1.29
Severely obese	0.82	0.62, 1.08	0.87	0.76, 0.99	0.87	0.76, 1.12
GDM						
Underweight	1.31	0.85, 2.04	1.14	0.82, 1.52	1.14	0.65, 1.88
Normal weight	1.00	referent	1.00	referent	1.00	referent
Overweight	2.56	2.10, 3.11	2.09	1.82, 2.40	2.09	1.63, 2.67
Obese	5.18	4.18, 6.53	3.97	3.48, 4.52	3.97	3.06, 5.11
Severely obese	8.02	6.43, 10.01	5.80	5.26, 6.41	5.80	5.26, 7.31
Preeclampsia						
Underweight	0.93	0.66, 1.33	0.94	0.73, 1.19	0.94	0.61, 1.40
Normal weight	1.00	referent	1.00	Referent	1.00	referent

	Conventional result [a]		Bias analysis result [b]		Total error result [c]	
	Adjusted [d] odds ratio	95% confidence interval	Adjusted [d] point estimate	95% simulation interval	Adjusted [d] point estimate	95% simulation interval
Overweight	1.47	1.25, 1.74	1.35	1.20, 1.52	1.35	1.10, 1.66
Obese	2.24	1.84, 2.73	1.94	1.71, 2.19	1.94	1.53, 2.45
Severely obese	2.30	1.82, 2.90	2.07	1.87, 2.30	2.07	1.87, 2.60

[a] Estimates are generated from a conventional logistic regression model, without accounting for misclassification.

[b] Estimates reflect adjustment for the exposure misclassification bias and additional uncertainty contributed by classification errors (i.e., systematic error only).

[c] Estimates account for this misclassification bias as well as random error.

[d] Adjusted for maternal race/ethnicity, age, marital status, education, parity, smoking status, clinic/private patient, and delivery year.

[e] Underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5 to 24.9 kg/m^2), overweight (BMI 25.0 to 29.9 kg/m^2), obese (BMI 30-34.9 kg/m^2), and severely obese (BMI ≥35 kg/m^2).

Obesity (Silver Spring). Author manuscript; available in PMC 2011 November 1.

Table 3

Predictive Values for Self-Reported Body Mass Index Category Among Nonpregnant Women Aged 16-44 Years, National Health and Nutrition Examination Survey, 1999-2006 (n=5,577).

		Measured BMI [a]				
		Underweight [b]	**Normal weight**	**Overweight**	**Obese**	**Severely obese**
Self-reported BMI [c]	Underweight, PV [d]	**0.76**	**0.24**	-	-	-
	Normal weight, PV	**0.03**	**0.85**	**0.11**	**0.003**	**0.001**
	Overweight, PV	-	**0.08**	**0.76**	**0.15**	**0.01**
	Obese, PV	-	**0.001**	**0.08**	**0.72**	**0.19**
	Severely obese, PV	-	**0.001**	**0.003**	**0.07**	**0.93**

Abbreviations: BMI, body mass index; PV, predictive value.

[a] BMI based on measured weight and height.

[b] Underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5 to 24.9 kg/m^2), overweight (BMI 25.0 to 29.9 kg/m^2), obese (BMI 30-34.9 kg/m^2), and severely obese (BMI ≥35 kg/m^2).

[c] BMI based on self-reported weight and height.

[d] PV is calculated as the probability that women in each self-reported BMI category are truly underweight, truly normal weight, truly overweight, truly obese, and truly severely obese. Estimates were weighted to account for the complex sampling design.

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