

*Original Article***Reducing the risk of low or high birth weight for women with low or high body mass index under the care of high quality hospital by using instrumental variable**Manoochehr Babanezhad^{1,2*}

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Abstract

Background and purpose: Women with low (high) pre-pregnancy body mass index (BMI) recently delivered infants with approximately normal or close to normal birth weights under the high quality of prenatal care. This study estimated the effect of pre-pregnancy BMI when concerns about the effects of different quality levels of prenatal care and the health status of mothers and their infants existed.

Materials and Methods: The sample consisted of the female patients who referred to one of the two hospitals with different quality levels of prenatal care in Gorgan. The logistic mixed effect model and Chi-square test did not show any significant effect of low (high) BMI on the risk of low (high) birth weight. Then, the two-stage residual inclusion instrumental variable (IV) method was used to estimate the effect of BMI in order to overcome the effects of the levels of quality care and the health status of the mothers and their infants.

Results: Adjusted IV analysis revealed that women with a low BMI experienced an approximately 18% (RR=0.82; 95% CI (0.69, 0.97)) reduction in the risk of delivering a LBW infant and women with a high BMI experienced an approximately 26% (RR=0.74; 95% CI (0.57, 0.96)) reduction in the risk of delivering a HBW infant when they were under the care of a high quality hospital.

Conclusion: This study revealed that the effect of BMI is confounded by the effects of quality of care and the health status of the mothers and their infants. Further, these results contributed to providing the conditions in improving the health status of mothers and their infants during pregnancy in local areas.

Keywords: Body mass index; Instrumental variable; Quality of care; Low and high birth weights.

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1. Introduction

For years, pre-pregnancy Body Mass Index (BMI) has been used as the major risk factor index for pregnancy outcomes, such as Infant Birth Weight (IBW) (1-11). Plenty of research has been performed to assess the effects of different BMI categories on the risks of delivering Low Birth Weight (LBW) and High Birth Weight (HBW) infants (1-9). However, there is still controversy about the cut-off points for the range of low (high) BMI associated with the risk of LBW (HBW) infant for all women in different nations (12-13). Most of the studies showed that women with a low pre-pregnancy BMI increased the possibility of having an LBW infant, and women with a high pre-pregnancy BMI increased the possibility of having an HBW infant (1-6). For instance, (1) showed a significant risk of LBW infant among women with BMI<19.9, and a significant risk of macrosomia among women with BMI>26, in Seattle, Tacoma, and Washington. Also, (2) showed that women with BMI=25–29 experienced a significant risk of macrosomia in Denmark. Moreover, (3) revealed women with BMI=24–27.9 experienced a significant risk of macrosomia in China. In another study carried out by (4), it was shown that the infants of mothers with BMI<18.5 had more than twice the risk of LBW as compared with those of mothers with BMI=18.5–25 in Oman. On the other hand, (5) found that there was no difference between the low birth rate among the participants with BMI≤19 as compared with the participants with BMI>19 among Pakistani women who delivered in the public hospitals, whereas in Iran, (6) showed that women with BMI≥ 25 had a higher incidence of macrosomia

than women with BMI< 25. While these explorations established effective guidelines for the improvement of mother's and infant's healthcare strategies at different national and local levels (1-8), some of them are still prone to the lack of controlling the effect of quality of prenatal care and the health status of mothers and their infants on the risk of infant birth weight. For instance, the problem of ignoring the care levels of two different hospitals was discussed by (6). In their study, the effect of BMI on the risk of LBW (LBW) was contaminated by the hospital care levels and by the unobserved health status of the mothers and their infants (6, 14-15). Their primary results showed some indication that LBW (HBW) was affected by the quality level of hospital care and unobserved health status of the mothers and their infants in addition to mother's pre-pregnancy BMI. Thus, measuring simply the risk of LBW (HBW) may not yield a consistent estimate due to the existence of the latter factors associated with LBW (HBW) which were omitted from the analysis (16-19). As a result, the question that the researchers attempted to answer was whether or not women with a low (high) BMI reduced the risk of a LBW (HBW) infant when they were under the care of a high quality hospital by controlling the effect of unobserved health status. To answer the question, the researchers used a statistical method, namely Instrumental Variable (IV) method that accounts for the effect of quality of care on the presence of unobserved health status of the mothers and their infants (16-19). Using IV methods has already started in econometrics and health outcome research. Some studies have recently succeeded in

establishing geographic location as IV to obtain the effectiveness of the hospital care (20-25). For instance, the authors in (20) proposed differential distance as IV to determine the effect of more intensive treatments on mortality in elderly patients with acute myocardial infarction. However, the geographic location was widely designed as IV, but there were concerns that the invalid and weak IV fail to accomplish a consistent estimate (26-30). Hence, the main aim of this study was to examine whether or not women with a low (high) BMI reduce the risk of delivering a LBW (HBW) infant when they were under the care of a high quality hospital by controlling the health status of the mothers and their infants.

2. Material and Method

The participants of the current study were the women referred at ≤ 20 weeks of gestation in one of the two hospitals with different levels of quality of prenatal care in a city of Iran with expected delivery dates between July 2011 and May 2013. There were actually nine hospitals involved in the study. Three of the hospitals were public managed by Golestan University of Medical Sciences, and six of them were private. The eligible participants were the women who followed the prenatal care of a hospital and planned to deliver at the same hospital. Women were interviewed by trained health workers during the first visit. Maternal information, such as weight in early pregnancy, height, age, last menstrual period, parity, illness, education, occupation, smoking, use of alcohol, and history of abortion and stillbirth, and residence address, were collected using a standard questionnaire. Pre-pregnancy weight was also self-reported or measured in the first visit. Pre-

pregnancy BMI was calculated by pre-pregnancy weight divided by squared height. The sample also received some manuals with instructions for prenatal and postnatal care regarding their BMI categories and their observed health status. At the same time, Gestational Weight Gain (GWG) was measured by differencing between the pre-pregnancy weight and the weight before delivery. Type of delivery, such as cesarean, post-term, pre-term, as well as infant information, such as weight and sex were recorded. The permission for collecting the data in this study was approved by Golestan University of Medical Sciences. Pregnancy outcomes were LBW (a live born infant of < 2.5 kg), normal birth weight (2.5–4kg), and HBW (a live born infant of > 4 kg). Normal birth weight was considered as the reference level. Estimating the effect of BMI on the risk of IBW often relies on the classification of the healthy and unhealthy pre-pregnancy weight segments based on the World Health Organization guidelines. Guidelines are often presented by the strong evidence of the association between BMI and the risk of IBW. Then, BMI is often categorized into 4 classes according to the WHO guidelines as: underweight (BMI < 19.8), normal weight (BMI=19.8–25), overweight (BMI=25–30), and obese (BMI ≥ 30). The scientific review of the WHO guidelines showed that there was still controversy about the cut-off points for the range of low (high) BMI associated with the risk of LBW (HBW) infant in clinical practice for all women in different nations [12-13]. Therefore, in the present study, two levels of BMI were established as two continuous treatments corresponding to the two considered

outcomes. The researchers considered $BMI_1 = BMI \leq 25$ (kg/m^2) as low BMI and $BMI_2 = BMI > 25$ (kg/m^2) as high BMI. The former segment was considered because there were observed some women even with $BMI = 19.9 - 25$ (kg/m^2), and experienced the risk of delivering an LBW infant.

IV is a variable that is associated with the study treatment, e.g. BMI (assumption 1), but neither directly related to the study outcome, e.g. IBW, nor indirectly related through confounding the treatment and outcome (assumption 2). The latter implies that IV is associated with IBW through only its association with BMI. The women in the current study were enrolled in one of the two hospitals with different levels of care quality which are all shown in Table 1.

The dimensions of the quality level of a hospital are often measured based on the medical facilities, such as having connoisseur specialists and trainers, bed availability, technological resources, and providing comprehensive care even in emergency situations. These features are accepted among the local healthcare physicians to determine the quality level of a hospital center (14-15). By examining the aforementioned features, the private hospitals were accepted as high quality level hospitals in our study areas (15). Furthermore, the highly competitive market in the private hospital industry has caused increasing pressure on them to provide services with higher quality than those public hospitals.

The participants of the study selected hospitals under the two hypotheses, the distance of their home location and the quality level of care. They, in fact, tended to select the nearest high quality hospital. Thus, the location of

participants and hospital quality independently affected the hospital choice.

In order to proceed through the IV method, a variable should be found that has no direct effect on IBW and does affect the likelihood of BMI. Therefore, distance is defined by calculating the distance in kilometers (km) between the women's home location and the nearest private hospital minus the distance in km between the women's home location and the nearest public hospital by using GPS. This, in fact, is differential distance rather than direct distance, because it is likely to influence the choice of the hospital that women selected, but is not presumably associated with other factors that could affect IBW. Specifically, the differential distance between hospitals and women's home location was used as an IV, which outlines the underlying IV assumptions necessary for obtaining a consistent estimate. Afterwards, the IV method was compared with the logistic mixed-effect model with random intercept and random slope for hospital levels.

Then, women were grouped into two classes of distance: ≤ 2.75 and > 2.75 kms, which was established based on the mean (2.75kms) differential distance. The women were, then, divided into two groups of close to and far from the private hospitals. This provided some insights into the IV mechanism.

Two-stage residual inclusion IV estimator

In the present study, the researchers considered BMI_1 and BMI_2 as two continuous treatments, LBW and HBW as two binary outcomes, and Z as binary IV. The two-stage residual inclusion IV estimation method was also established in two stages (31). Hence, the current study

examined the extent to which differential distance was associated with BMI₁ (BMI₂) at first stage by fitting the following linear regression model:

$$X = \beta_0 + \beta_1 Z + W\theta + \varepsilon(1)$$

Where X is BMI₁ (BMI₂), β_0 is the intercept, β_1 is the effect of Z on BMI₁ (BMI₂), W is the characteristics of the mothers and their infants, and θ is the parameter of the effect of W, and ε is error term. Then, the researchers fitted the logistic regression model of binary outcome Y on $\hat{\varepsilon} = X - \hat{X}$ (predicted residual values of model (1)) and W as follows:

$$\text{logit}\{P(Y=1)\} = \psi_0 + \psi_1 \hat{\varepsilon} + W\gamma + \varepsilon(2)$$

where Y is LBW (HBW), ψ_0 is intercept, ψ_1 is the log risk ratio (RR) of the effect of BMI₁ (BMI₂), γ is the vector parameters of the effect of W, ε is the error term, and $\log\text{it}(p) = \log(p/(1-p))$. Note that parameter ψ_1 represents the average change in outcome LBW (HBW) for a change in BMI₁ (BMI₂) among women whose BMI₁ (BMI₂) are affected by Z levels. To account for uncertainty in $\hat{\varepsilon}$ and in order to consistently estimate 95% confidence interval (CI) of ψ_1 , the robust estimation approach was used to estimate the standard error of $\hat{\psi}_1$ (31-32). Note that the two-stage residual inclusion IV method requires a consistent estimator of the first stage residuals. Since model (1) consistently estimates $\hat{\varepsilon}$, it is an appropriate choice for estimating $\hat{\psi}_1$ (31). It should also be noted that W is included in the first stage model because it is exogenous and so excluding W would lead to a loss in efficiency or consistency of the IV estimators (31-32).

3. Results

For analyzing the collected data, of 1541 initial participants, 246 persons were missing. Therefore, 1295 mothers and their infants were used in the analysis in which 39.77% and 60.23% were admitted to private and public hospitals, respectively. To perform direct comparisons, we grouped the women across two different hospital levels (Table 1).

Table 1. pre-pregnancy body mass index categories, distribution (%) of low birth weight and high birth weight, and distribution (%) of the characteristics of the mothers and the infants in the private and public hospitals-north east areas of Iran

	Private n=515	Public n=780	Unadjusted P. value
Treatments			
Mean (SD)			
BMI ₁	20.08 (2.45)	22.01 (1.70)	<0.01
BMI ₂	31.45 (3.23)	28.14 (3.84)	<0.01
Outcomes			
%			
LBW	5.83	11.03	0.04
HBW	9.36	15.00	<0.01
Characteristics of mothers and infants			
Mean (SD)			
GWG	11.55 (4.62)	12.20 (4.45)	0.11
Age	27.05 (5.53)	24.95 (4.92)	<0.01
%			
Cesarean	31.07	51.15	<0.01
Post-term	5.24	10.64	<0.01
Pre-term	6.02	13.33	<0.01
Parity			
0	38.06	46.02	<0.01
1	52.81	42.31	<0.01
2	7.38	10.13	0.11
≥3	1.75	1.54	0.94
Illness	29.13	15.90	<0.01
Education			
≤school	18.45	22.31	0.11
High school	34.75	43.72	<0.01
University	46.80	33.97	<0.01
Occupation	32.82	18.85	<0.01
Abortion	17.28	4.36	<0.01
Stillbirth	13.59	3.72	<0.01
Infant sex			
Boy	53.20	52.56	0.86
Girl	46.80	47.44	0.86

*SD=Standard deviation.

BMI₁*= BMI≤ 25 kg/m²; BMI₂*= BMI>25 kg/m².

Note that the women were reported to be non-smokers, non-drinkers, and non-drug users.

As Table 1 shows, the women in private hospitals in comparison with the women in the public hospitals were markedly older (27.05 vs. 24.95 years in average) and with the higher prevalence of illness (29.13 vs. 15.90). Further, there were large unadjusted differences

between the observed characteristics of mothers, and also in LBW prevalence (5.83 vs. 11.03), and in HBW prevalence (9.36 vs. 15). It implied that the dissimilarity in LBW (HBW) may not have occurred just through the BMI₁ (BMI₂) effect. It was, therefore, likely that the

unadjusted effect of BMI₁ (BMI₂) on LBW (HBW) rate was overestimated partly because of the underlying differences in the two hospital levels of care and also partly due to the unobserved health status of the mothers and their infants between two groups of women. The participants in the current study were grouped based on the mean differential distance (2.75 km) from the nearest private hospital to provide IV mechanism. That is, the women

who faced a differential distance of 2.75 km or less, either had a private hospital as their nearest hospital or had to travel less than 2.75 km further than the distance to their nearest hospital to reach a private hospital. The greater the differential distance, the less likely it was that a woman would be admitted to a private hospital.

Table 2. Pre-pregnancy body mass index categories, distribution (%) of the Low Birth Weight and the High Birth Weight, and distribution (%) of the characteristics of the mothers and the infants according to the two groups of differential distance-north east areas of Iran

	Differential distance ≤2.75 kms (n=583)	Differential distance >2.75 kms (n=712)	Unadjusted P. value
Treatments			
Mean (SD)			
BMI ₁	21.69 (2.31)	22.30 (2.09)	<0.01
BMI ₂	30.24 (4.85)	29.05 (3.15)	<0.01
Outcomes			
(%)			
LBW	7.55	9.55	0.13
HBW	11.49	14.75	0.11
Admit to private hospital (%)	67.70	16.85	<0.001
Characteristics of mothers and infants			
Mean (SD)			
GWG (kg)	11.65 (3.36)	11.85 (3.92)	0.11
Age (year)	26.25 (4.71)	25.98 (5.21)	0.10
(%)			
Cesarean (%)	40.82	45.08	0.14
Post-term (%)	7.03	9.69	0.11
Pre-term (%)	8.92	11.66	0.13
Parity (%)			
0	41.17	44.24	0.29
1	49.05	44.39	0.11
2	7.89	9.97	0.23
≥3	1.89	1.40	0.64
Illness (%)	23.33	19.38	0.11
Education (%)			
≤school	21.27	20.37	0.74
High school	37.56	42.27	0.10
University	41.17	37.36	0.18
Occupation (%)	26.42	22.75	0.14
Abortion (%)	10.98	8.29	0.12
Stillbirth (%)	8.75	6.74	0.22
Infant sex (%)			
Boy	54.03	51.83	0.46
Girl	48.03	46.49	0.62

*SD = Standard deviation.

BMI₁* = BMI ≤ 25 kg/m²; BMI₂* = BMI > 25 kg/m².

Table 2 shows that the differences between the women across differential distance were substantially less marked than those observed in Table 1. Table 2 also shows that 67.7% of the participants relatively close to private hospitals selected private hospitals, and only 16.85% of them who were close to public hospitals selected private hospitals. Moreover, the women with lower and higher BMI tended to go to the nearest private hospitals. Further, the women who lived near the private hospitals experienced a lower rate of LBW (HBW) as compared with those who lived near the public hospitals. That is, with a 50.85% increase in the percentage of women admitted to the private hospital, a decline of approximately 2% and 3.26% occurred in LBW and HBW rates, respectively. A balance was also documented between the observed characteristics of the mothers in these two groups. It should be noted that the significant differences between BMI₁ of these two groups of women (21.69 vs. 22.30, p. value<0.01) and between BMI₂ (30.24 vs. 29.05, p. value<0.01) implied that the differential distance was an independent predictor of BMI (the first IV assumption was

satisfied) (28-31). However, since the second IV assumption was untestable, the association between the differential distance and the outcomes was also tested. That is, Z-LBW and Z-HB Risk Ratios (RRs) and their 95% CI were estimated respectively as RR=0.70 (95% CI: 0.44, 1.11), and RR=0.74 (95% CI: 0.52, 1.06). Thus, there was strong evidence for the null hypothesis of the direct effect of differential distance on LBW and HBW (the second IV assumption was satisfied).

The researchers also performed the two-stage residual inclusion IV analysis (31), so as to reveal the effect of BMI₁ (BMI₂) on LBW (HBW) by the adjusted risk ratio (RR) and its 95% CI, as shown in Table 3.

Table 3. pre-pregnancy body mass index on the risks of Low Birth Weight and High Birth Weight by the Instrumental Variable (IV) method and the logistic mixed-effect model – In north east areas of Iran

	Outcomes	Adjusted RR 95% CI
Two-stage IV analysis^R		
BMI₁	LBW	0.82 (0.69, 0.97)*
BMI₂	HBW	0.74 (0.57, 0.96)*
Logistic mixed-effect model analysis		
BMI₁	LBW	1.07 (0.95, 1.21)
BMI₂	HBW	1.10 (0.97, 1.25)

^RThe 95% CIs were based on Robust Standard Errors.

*P.value<0.05.

BMI₁*= BMI≤ 25 kg/m²; BMI₂*= BMI>25 kg/m².

Table 3 shows that the risk of having a LBW infant among women with BMI₁ who lived near the private hospital as compared with those who lived near the public hospital was RR=0.82 (95% CI: 0.69, 0.97). This implies that the women with BMI≤25 who were under the care of a private hospital experienced an approximately 18% reduction in the risk of delivering a LBW infant as compared with the women with the same BMI who were under the care of a public hospital, adjusted the mothers and their infants' characteristics. In this case, Z had a significant effect on BMI₁ with an F-statistic =19.79 and R²_a = 0.23 at the first stage analysis, indicating that the differential distance was a fairly strong predictor for BMI₁ (26-30). Likewise, the results showed that the risk of having an HBW infant among the women with BMI₂ who lived near the private hospital as compared with those who lived near the public hospital was RR=0.74 (95% CI:0.57, 0.96). This implied that the participants with BMI>25 who were under the care of a private hospital experienced an approximately 26%

reduction in the risk of delivering an HBW infant as compared with the participants with the same BMI who were under the care of a public hospital, adjusted the mothers and their infants' characteristics. In this case, Z had a significant effect on BMI₂ with an F-statistic=18.46 and R²_a = 0.21 at the first stage analysis, indicating that the differential distance was a fairly strong predictor for BMI₂ (26-30). Note that we estimated the two-stage IV confidence interval using robust standard error which was narrower than the other methods such as bootstrap or delta methods (31-32). Different results were obtained in the current study through using the logistic mixed-effect model. The associational estimate of RR=1.07 (95% CI: 0.95, 1.21) showed no significant reduction in the risk of having an LBW infant for women with BMI≤25 in the private hospital as compared with those women in the public hospital. Similarly, the associational estimate of RR=1.10 (95% CI: 0.97, 1.25) showed no significant reduction in the risk of having HBW infant for women with BMI>25 in the private

hospital as compared with the women in the public hospital. It should be noted that the latter model was applied with random intercept and the random slope for hospital levels. At the same time, the latter estimates had narrower confidence intervals than the wide confidence intervals of IV analysis. This was, in fact, due to the small proportion of the variation in BMI as explained by hospital levels.

4. Discussion

The present study examined the effect of pre-pregnancy BMI on the risk of LBW (HBW) by controlling the effects of hospital care levels and the health status of mothers and their infants. The researchers' interest in identifying the latter subject stemmed from the fact that women with unfavorable (low or high) BMI have recently delivered infants with approximately favorable (normal or close to normal) birth weights at the hospitals with high quality of care. Hence, the current research attempted to answer the question whether the quality levels of hospital care affects the risk of LBW (HBW) for women with low (high) pre-pregnancy BMI through controlling the health status of mothers and their infants. The research areas included a city and its countryside in Iran, which suffered from the problem of infants with low (high) birth weights [6, 10]. Hence, the two-stage residual inclusion IV method was used in the study, and the results showed that the women with low (high) BMI who were under the care of a high quality hospital reduced the risk of delivering a LBW (HBW) infant to 18% (to 26%), even though 23.33% of them had/have illness experience. It should also be noted that these groups of women had even lower (higher) BMI than the women who were

under the care of a public hospital. It was expected that the women with lower (higher) BMI would have experienced increased risk of LBW (HBW) infants as shown by the previous study results (1-4). The considered IV estimator was similar to the standard two-stage IV method, except that in the second-stage, the endogenous variable was not replaced by the first-stage predictor. Instead, the first-stage residuals were included as the additional regressors (31). Further, based on the theoretical properties of the estimators, the IV estimation method posed a particular statistical challenge in the case of binary outcomes. Therefore, Risk Ratio (RR) instead of Odds Ratio (OR) was estimated. The former criterion allowed consistent estimation of the continuous treatment effect (31-32). For comparison purpose, the logistic mixed-effect model was used by including the hospital levels as mixed-effect. The findings indicated no significant reduction in the risk of an LBW (HBW) infant among the women with low (high) BMI. This was because of the fact that the latter model did not properly account for the differences in the quality levels of hospital care and the health status of the mothers and their infants. Further, GWG was considered as a potential confounder fact or for the purpose of assessing the association between GWG and BMI. Since GWG indicates maternal weights during pregnancy and is always suspected to modify the effect of BMI (3-4), BMI₁ (BMI₂) was stratified on GWG as a treatment in the analysis. There were documented no significant effect modifications by GWG on BMI₁ (BMI₂) in estimating the risk of LBW (HBW). Finally, it is now believed that the results of the present

study are more broadly useful as they suggest, and may be incorporating, the possibility that a little prior information on a stronger IV may yield substantial efficiency improvements for the target parameter ψ_1 in the model (2).

The current study also encountered some limitations. First, the IV methods have often been applied in large databases. In this study, the sample sizes were 518 individuals in estimating the BMI₁ effect on LBW and 673 individuals in estimating the BMI₂ effect on HBW. The IV estimators are consistent here but may not be unbiased. This underscores the necessity of using large samples. On theoretical grounds, it is, accordingly, recommended to make improvement in the association between differential difference and maternal pre-pregnancy BMI by increasing the sample sizes, which could result in better adjustment across women with different pre-pregnancy BMI categories. Although the large variance of the IV estimate at smaller sample sizes may not influence the validity of the IV estimates, it principally improves the efficiency of IV estimates. The second limitation was the observed differences within the private hospitals. As mentioned earlier, the sample for this study were admitted to six private hospitals with a probability of heterogeneity among them which has not been accounted for in this study. The third limitation was that some women lived in the countryside of the study area, some others attended a private hospital during five weeks of gestation due to emergency problem, and they had to have monthly visits. Hence, they were given some medication in addition to the common care, suggesting that the greater availability of hospital care may reduce the risk

of IBW. And, the final limitation of the study was that the majority of women who selected private hospitals were from urban areas and had insurance coverage. This study revealed that the effect of BMI was confounded by the effects of quality of care and the status of mothers and their infants. Further, the results of the current research contributed to providing the conditions for improving the health status of mothers and their infant during pregnancy in local areas.

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Conflict of interest

The Author has no conflict of interest.

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