PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of Multiparity on Left Ventricular Diastolic Dysfunction in Women: Cross Sectional Study of the Korean Women's Chest Pain Registry (KoROSE)
AUTHORS	Kim, Hyun-Jin; Kim, Myung-A; Kim, Hack-Lyoung; Shim, Wan Joo; Park, Seong-Mi; Kim, Mina; Yoon, Hyun Ju; Shin, Mi-Seung; Hong, KS; Shin, Gil Ja; Kim, Yong-Hyun; Na, Jin Oh; Jeong, Jin-Ok

VERSION 1 – REVIEW

REVIEWER	Keskin, Muhammed Sultan Abdulhamid Han Training and Research Hospital, Istanbul
REVIEW RETURNED	06-Oct-2018

GENERAL COMMENTS	Dear Editor, Thank you assigning as a reviewer. This study is about the association of long-term effect of the number of parity and diastolic function in women. However, there are some article about the temporary changes in diastolic function in pregnancy; there is not enough evaluations about the long-term effect of pregnancy. The article is relatively novel in this topic. Although I have several concerns about the study. 1. There is a comprehensive study in this topic with profound echocardiographic examinations. I recommend to cite and discuss this article: Keskin M. et al. Am J Cardiol. 2017 Jul 1;120(1):154-159.Relation of the Number of Parity to Left Ventricular Diastolic Function in Pregnancy. 2. The main enrollment for this study was made after coronary angiography. We could not see the any details of CAG despite coronary artery disease's serious effect on diastolic functions. 3. Propagation velocity, pulmonary vein inflows and especially tricuspid valve insufficiency and pulmonary artery systolic pressure are important variables when determining diastolic dysfunction. Please demonstrate these additional variables if possible. 4. It is very important to reveal the diastolic functions in nulliparous women. Because these women have not been affected by any parity changes. And logistic regression analyses should be reperformed according to this group. 5. In statistical analysis, the authors did not check the normality of groups and used t test for all variables. I recommend authors to get a help in statistics. 6. In discussion section, the authors should give some more details about the possible effects multiparity on diastolic functions.

REVIEWER	C. Noel Bairey Merz MD Cedars-Sinai Smidt Heart Institute, Los Angeles, California, USA

REVIEW RETURNED	15-Oct-2018

GENERAL COMMENTS	1. The statement "Left ventricular (LV) diastolic dysfunction has been known to occur early in all cardiovascular diseases and is also related to cardiovascular mortality.1 2" is not well-accepted, nor appropriately referenced. Citations should be original manuscripts that are to the point, and not review articles or editorials. 2. The lack of women with parity data is substantially greater than 20%, which is one indication of a "poor quality" dataset. 3. Do not repeat data in Tables or Figures in the text. 4. Parity is typically confounded by education and socio-economic status, e.g. higher parity is associated with lower education and SES. This needs to be added to the analyses or reported as a major limitation. 5. Parity and CVD is controversial in the literature with lower CVD rates being observed in 1-4 births compared to higher rates for 0 and above 4. This needs to be analyzed and appropriate prior work cited Lv 2015, Catov 2008).

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: #1
This study is about the association of long-term effect of the number of parity and diastolic function in women. However, there are some article about the temporary changes in diastolic function in pregnancy; there is not enough evaluations about the long-term effect of pregnancy. The article is relatively novel in this topic. Although I have several concerns about the study.

[Comment #1]
There is a comprehensive study in this topic with profound echocardiographic examinations. I recommend to cite and discuss this article: Keskin M. et al. Am J Cardiol. 2017 Jul 1;120(1):154-159.Relation of the Number of Parity to Left Ventricular Diastolic Function in Pregnancy.

[Response]
Thank you for the valuable comment. Reviewer's comment was well taken. We reviewed the article '*Relation of the Number of Parity to Left Ventricular Diastolic Function in Pregnancy*' in detail. This study evaluated the long-term changes in maternal cardiovascular system after pregnancy and grand multipariy has been found as an independent risk factor of LV diastolic dysfunction. Therefore, we cited and discussed this article in **Discussion** section - sub-heading **LV diastolic dysfunction and multiparity** – and **Reference** section as following.

Added sentences in **'LV diastolic dysfunction and multiparity'** of **Discussion** section,
"There have been several studies showing long-term changes in maternal cardiovascular system after pregnancy, and Keskin M et al. have demonstrated that grand multiparity over 4 in Turkish population is an independent risk factor for LV diastolic dysfunction.[16]"

And added reference in **Reference** section,
16. Keskin M, Avsar S, Hayiroglu MI, et al. Relation of the Number of Parity to Left Ventricular Diastolic Function in Pregnancy. *Am J Cardiol* 2017;120(1):154-59. doi: 10.1016/j.amjcard.2017.03.244.

[Comment #2]
The main enrollment for this study was made after coronary angiography. We could not see the any details of CAG despite coronary artery disease's serious effect on diastolic functions.

[Response]

We appreciate the reviewer's point and thank you for your thoughtful comment. KoRean wOmen'S chest pain rEgistry (KoROSE) consists of all patients with chest pain who had undergone coronary angiography regardless of coronary artery disease. Unfortunately, we focused on the association between LV diastolic dysfunction and multiparity in this study, so the results of coronary angiography were not described in detail, but only the prevalence of coronary artery disease confirmed by coronary angiography as showed in Table 1 was described. We used the traditional angiographic imaging definition for coronary artery disease, which defining focal coronary artery stenosis of 50% or more diameter.
Therefore, we added the sentence about coronary artery disease in **Methods** section as following and added reference in **Reference** section as following.

In '**Clinical and Laboratory Assessments'** of **Methods** section,
"The traditional angiographic imaging definition was used for coronary artery disease, which defining focal coronary artery stenosis of 50% or more vessel diameter.[13]"

In **Reference** section,
13. Rumberger JA. Coronary Artery Disease: A Continuum, Not a Threshold. *Mayo Clin Proc* 2017;92(3):323-26. doi: 10.1016/j.mayocp.2017.01.009

[Comment #3]
Propagation velocity, pulmonary vein inflows and especially tricuspid valve insufficiency and pulmonary artery systolic pressure are important variables when determining diastolic dysfunction. Please demonstrate these additional variables if possible.

[Response]
Thank you for the valuable comment. As your valuable comment, propagation velocity, pulmonary vein inflows SD ratio, tricuspid valve regurgitation peak velocity and pulmonary artery systolic pressure are important variable for evaluating diastolic dysfunction. We had already shown the pulmonary artery systolic pressure as right ventricular systolic pressure in Table 2. Also, we analyzed the difference of the tricuspid valve regurgitation peak velocity between low-parity group and multi-parity group additionally and added the values in Table 2. Unfortunately, there were no available data about propagation velocity, pulmonary vein inflows in KoROSE registry. If we had the data about propagation velocity, pulmonary vein inflows, the contents would have been more delicate. Therefore, we revised the Table 2 as following.
Table 2. Echocardiographic measurements

	All (N = 960)	Low-parity group, Parity < 3 (n = 302)	Multiparity group, Parity ≥ 3 (n = 658)	P-value
RVSP, mmHg	32.1 ± 9.6	29.9 ± 8.6	33.0 ± 9.9	< 0.001
TR peak velocity, cm/s	2.3 ± 0.3	2.2 ± 0.3	2.3 ± 0.3	0.038

RVSP, right ventricular systolic pressure; TR, tricuspid regurgitation

[Comment #4]
It is very important to reveal the diastolic functions in nulliparous women. Because these women have not been affected by any parity changes. And logistic regression analyses should be reperformed according to this group.

[Response]
Thank you for the important comment. Reviewer's comment was well taken. We investigated how many nulliparous women were among the total 960, and only 27 women were nulliparous. We performed the logistic regression to evaluate the univariable and multivariable predictor for LV diastolic dysfunction except nulliparous group (parity = 0, n =27) as below.

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Multiparity (n ≥ 3)	2.97	2.029-4.343	< 0.001	1.81	1.046-3.133	0.0324
Age (> 60 yr)	14.67	8.917-24.117	< 0.001	9.84	5.031-19.232	< 0.001

BMI ≥ 25	1.59	1.076-2.357	0.020	1.78	1.033-3.069	0.038
Heart rate	1.03	1.012-1.043	0.001	1.02	1.000-1.046	0.049
Hypertension	5.61	3.618-8.694	< 0.001	2.62	1.409-4.870	0.002
Diabetes mellitus	10.58	4.246-26.359	< 0.001	5.78	1.297-25.734	0.021
Coronary artery disease	4.43	2.930-6.705	< 0.001	1.87	1.055-3.297	0.032
WBC	1.00	1.000-1.000	<0.001	1.000	1.000-1.000	0.901

As shown in the table above, multiparity (n ≥ 3) was also found to show a 1.81-fold increased risk for LV diastolic dysfunction after adjusting for other relevant factors in group except nulliparous women. This result was similar to the logistic regression result for all 960 patients (OR 1.80, 95% CI 1.053-3.081, p = 0.032). It is assumed that the number of nulliparous women was so small in our registry and did not show any statistically significant difference. Therefore, after careful consideration, we decided not to revise the logistic regression analysis in Table 3.

[Comment #5]
In statistical analysis, the authors did not check the normality of groups and used t test for all variables. I recommend authors to get a help in statistics.

[Response]
Thank you for your attentive comments. Reviewer's comment was well taken. We checked the normality of continuous variables in each groups using Kolmogorov-Smirnov test. As a result, several variables did not show normal distribution. Therefore, we used Mann Whitney U-test to compare continuous variables which did not show normal distribution. And, the Student *t* test was used to compare continuous variables which showed normal distribution. We added sentences about statistics in methods section, and revised Table 1 and 2 after re-analysis as following.

In '**Statistical Analysis'** of **Methods** section,
"The Student *t* test was used to compare continuous variables."
Was changed to..
"The Student *t* test was used to compare continuous variables with normality and the Mann Whitney U-test was used to compare continuous variables without normality."

In **Results** section,
"The mean hemoglobin values were significantly lower in the multiparity patients than in the low-parity patients."
Was changed to..
"The mean hemoglobin values were significantly lower and the NT-proBNP values were significantly higher in the multiparity patients than in the low-parity patients."

In 'Table 1' of **Results** section,

	All (N = 960)	Low-parity group, Parity < 3 (n = 302)	Multiparity group, Parity ≥ 3 (n = 658)	P-value
Age (years)	63.5 ± 11.4	56.6 ± 11.5	66.6 ± 9.9	< 0.001
BMI, kg/m^2	25.2 ± 12.2	25.7 ± 19.8	25.0 ± 6.3	0.356
Waist circumference (cm)	78.4 ± 16.1	75.4 ± 16.3	79.6 ± 15.8	0.001
Systolic blood pressure, mm Hg	127.0 ± 20.4	126.3 ± 19.9	127.2 ± 20.6	0.577
Diastolic blood pressure, mm Hg	77.0 ± 12.8	77.1 ± 12.7	77.0 ± 12.9	0.869
Heart rate, beats/min	72.8 ± 15.8	73.7 ± 16.2	72.4 ± 15.7	0.253
Diabetes mellitus, n (%)	212 (22.1)	51 (18.8)	161 (27.1)	0.009
Hypertension, n (%)	508 (52.9)	134 (48.2)	374 (61.2)	<0.001
Dyslipidemia, n (%)	193 (20.1)	67 (22.2)	126 (19.1)	0.436
Atrial fibrillation, n (%)	45 (4.7)	9 (3.5)	36 (5.9)	0.136

Coronary artery disease, n (%)	519 (54.1)	121 (47.3)	398 (65.5)	<0.001
Current smoking, n (%)	30 (3.1)	10 (3.3)	20 (3.0)	0.897
ABI, Rt	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	0.788
ABI, Lt	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	0.579
Laboratory findings				
WBC, /ml	7411.6 ± 3078.2	7344.6 ± 2823.1	7441.1 ± 3185.8	0.672
Hemoglobin, g/dL	12.7 ± 4.5	13.2 ± 7.8	12.5 ± 1.5	0.029
Creatinine, mg/dL	0.9 ± 0.7	0.8 ± 0.7	0.9 ± 0.7	0.313
hs-CRP, mg/dL	1.8 ± 3.6	1.7 ± 3.0	1.8 ± 3.9	0.661
NT-proBNP, pg/mL	3594.0 ± 7313.8	2096.6 ± 5674.2	4054.0 ± 7707.4	0.074
Hemoglobin A1C, %	6.5 ± 1.3	6.4 ± 1.4	6.5 ± 1.3	0.592

Was revised to..

	All (N = 960)	Low-parity group, Parity < 3 (n = 302)	Multiparity group, Parity ≥ 3 (n = 658)	P-value
Age (years)	63.5 ± 11.4	56.6 ± 11.5	66.6 ± 9.9	< 0.001
BMI, kg/m^2	25.2 ± 12.2	25.7 ± 19.8	25.0 ± 6.3	0.223
Waist circumference (cm)	78.4 ± 16.1	75.4 ± 16.3	79.6 ± 15.8	<0.001
Systolic blood pressure, mm Hg	127.0 ± 20.4	126.3 ± 19.9	127.2 ± 20.6	0.571
Diastolic blood pressure, mm Hg	77.0 ± 12.8	77.1 ± 12.7	77.0 ± 12.9	0.976
Heart rate, beats/min	72.8 ± 15.8	73.7 ± 16.2	72.4 ± 15.7	0.203
Diabetes mellitus, n (%)	212 (22.1)	51 (18.8)	161 (27.1)	0.009
Hypertension, n (%)	508 (52.9)	134 (48.2)	374 (61.2)	<0.001
Dyslipidemia, n (%)	193 (20.1)	67 (22.2)	126 (19.1)	0.436
Atrial fibrillation, n (%)	45 (4.7)	9 (3.5)	36 (5.9)	0.136
Coronary artery disease, n (%)	519 (54.1)	121 (47.3)	398 (65.5)	<0.001
Current smoking, n (%)	30 (3.1)	10 (3.3)	20 (3.0)	0.897
ABI, Rt	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	0.808
ABI, Lt	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	0.753
Laboratory findings				
WBC, /ml	7411.6 ± 3078.2	7344.6 ± 2823.1	7441.1 ± 3185.8	0.859
Hemoglobin, g/dL	12.7 ± 4.5	13.2 ± 7.8	12.5 ± 1.5	0.007
Creatinine, mg/dL	0.9 ± 0.7	0.8 ± 0.7	0.9 ± 0.7	0.241
hs-CRP, mg/dL	1.8 ± 3.6	1.7 ± 3.0	1.8 ± 3.9	0.815
NT-proBNP, pg/mL	3594.0 ± 7313.8	2096.6 ± 5674.2	4054.0 ± 7707.4	0.026
Hemoglobin A1C, %	6.5 ± 1.3	6.4 ± 1.4	6.5 ± 1.3	0.309

In 'Table 2' of **Results** section,

	All (N = 960)	Low-parity group, Parity < 3 (n = 302)	Multiparity group, Parity ≥ 3 (n = 658)	P-value
Left ventricular end-diastolic dimension, mm	47.3 ± 5.0	46.3 ± 4.0	47.7 ± 5.4	< 0.001
Left ventricular end-systolic dimension, mm	30.2 ± 6.4	29.1 ± 5.2	30.7 ± 6.8	0.001
Interventricular septum thickness, mm	9.3 ± 1.6	9.1 ± 1.5	9.3 ± 1.7	0.028
Posterior wall thickness, mm	9.3 ± 4.3	9.1 ± 4.8	9.4 ± 4.0	0.396
Left ventricular ejection fraction, %	59.3 ± 9.8	61.0 ± 9.0	58.6 ± 10.0	0.001
Left ventricular mass index, g/m^2	101.8 ± 34.8	95.8 ± 29.3	105.0 ± 37.1	0.002

Left atrial dimension, mm	37.6 ± 6.3	35.9 ± 5.9	38.4 ± 6.3	< 0.001
E, cm/s	66.7 ± 20.1	69.1 ± 20.1	65.7 ± 20.0	0.028
A, cm/s	77.5 ± 22.8	71.7 ± 19.1	80.2 ± 23.9	< 0.001
E/A ratio	1.0 ± 0.6	1.0 ± 0.4	0.9 ± 0.7	0.037
Deceleration time, ms	212.1 ± 56.1	206.7 ± 60.5	214.5 ± 53.9	0.076
e´ septal, cm/s	5.9 ± 2.1	6.7 ± 2.4	5.5 ± 1.9	< 0.001
E/e´ ratio	12.6 ± 6.1	11.41 ± 5.26	13.14 ± 6.42	< 0.001
RVSP, mmHg	32.1 ± 9.6	29.9 ± 8.6	33.0 ± 9.9	< 0.001
Grade of left ventricular diastolic dysfunction, n (%)				< 0.001
Normal	148 (15.4)	77 (33.0)	71 (13.7)	
1	518 (54.0)	129 (55.4)	389 (75.2)	
2-3	84 (8.8)	27 (11.6)	57 (11.1)	

Was revised to..

	All (N = 960)	Low-parity group, Parity < 3 (n = 302)	Multiparity group, Parity ≥ 3 (n = 658)	P-value
Left ventricular end-diastolic dimension, mm	47.3 ± 5.0	46.3 ± 4.0	47.7 ± 5.4	< 0.001
Left ventricular end-systolic dimension, mm	30.2 ± 6.4	29.1 ± 5.2	30.7 ± 6.8	0.002
Interventricular septum thickness, mm	9.3 ± 1.6	9.1 ± 1.5	9.3 ± 1.7	0.008
Posterior wall thickness, mm	9.3 ± 4.3	9.1 ± 4.8	9.4 ± 4.0	< 0.001
Left ventricular ejection fraction, %	59.3 ± 9.8	61.0 ± 9.0	58.6 ± 10.0	0.004
Left ventricular mass index, g/m^2	101.8 ± 34.8	95.8 ± 29.3	105.0 ± 37.1	0.001
Left atrial dimension, mm	37.6 ± 6.3	35.9 ± 5.9	38.4 ± 6.3	< 0.001
E, cm/s	66.7 ± 20.1	69.1 ± 20.1	65.7 ± 20.0	0.019
A, cm/s	77.5 ± 22.8	71.7 ± 19.1	80.2 ± 23.9	< 0.001
E/A ratio	1.0 ± 0.6	1.0 ± 0.4	0.9 ± 0.7	<0.001
Deceleration time, ms	212.1 ± 56.1	206.7 ± 60.5	214.5 ± 53.9	0.030
e´ septal, cm/s	5.9 ± 2.1	6.7 ± 2.4	5.5 ± 1.9	< 0.001
E/e´ ratio	12.6 ± 6.1	11.4 ± 5.3	13.1 ± 6.4	< 0.001
RVSP, mmHg	32.1 ± 9.6	29.9 ± 8.6	33.0 ± 9.9	< 0.001
TR peak velocity, cm/s	2.3 ± 0.3	2.2 ± 0.3	2.3 ± 0.3	0.038
Grade of left ventricular diastolic dysfunction, n (%)				< 0.001
Normal	148 (15.4)	77 (33.0)	71 (13.7)	
1	518 (54.0)	129 (55.4)	389 (75.2)	
2-3	84 (8.8)	27 (11.6)	57 (11.1)	

[Comment #6]
In discussion section, the authors should give some more details about the possible effects multiparity on diastolic functions.

[Response]
Thank you for the valuable comment. As your thoughtful comment, it is important that the possible effects of multiparity on LV diastolic function. However, the exact mechanisms supporting the effect of multiparity on LV diastolic function have not been well known. Therefore, after careful consideration, we described the possible mechanism of multiparity effects on LV diastolic function focused on retention of water and sodium according to activation of the renin-angiotensin-aldosterone system and

myocardial hypertrophy according to change of estrogen in discussion section. We revised the sentences as following.

In '**LV diastolic dysfunction and multiparity'** of **Discussion** section,
"The mechanisms underlying the effect of repeated pregnancies on LV diastolic dysfunction are not well understood."
Was changed to..
"The mechanisms underlying the effect of multiparity on LV diastolic dysfunction are not well understood and are controversial."

"Our findings show that the prevalence of LV diastolic dysfunction increased according to parity number. Activation of the renin-angiotensin-aldosterone system and the adaptive changes in association with each pregnancy might lead to LV diastolic impairment. In addition, estrogen has been known to attenuate myocardial hypertrophy[17] and might be related to LV diastolic dysfunction in women with repeated pregnancies. Our study demonstrated that more multiparous patients than low-parity patients had LV hypertrophy, based on the increased LV mass index value."
Was changed to..
"Our findings show that the prevalence of LV diastolic dysfunction increased according to parity number. The possible mechanism of these findings by which repeated pregnancies effects LV diastolic dysfunction may be related to changes in various hormones. Retention of water and sodium according to the activation of the renin-angiotensin-aldosterone system and the adaptive changes in association with each pregnancy might lead to LV diastolic impairment. In addition, estrogen has been known to attenuate myocardial hypertrophy[19] and myocardial hypertrophy according to change of estrogen might be related to LV diastolic dysfunction in women with repeated pregnancies. Actually, our study demonstrated that more multiparous patients than low-parity patients had LV hypertrophy, based on the increased LV mass index value."

Reviewer: #2
[Comment #1]
The statement "Left ventricular (LV) diastolic dysfunction has been known to occur early in all cardiovascular diseases and is also related to cardiovascular mortality.1 2" is not well-accepted, nor appropriately referenced. Citations should be original manuscripts that are to the point, and not review articles or editorials.

[Response]
Thank you for your valuable comment. Reviewer's comment was well taken. LV diastolic dysfunction plays an important role in the development of heart failure. We deleted the 'reference #1. Leite-Moreira AF. Current perspectives in diastolic dysfunction and diastolic heart failure. *Heart* 2006;92(5):712-8. doi: 10.1136/hrt.2005.062950', and revised the sentences in introduction section as following.

In **Introduction** section,
"Left ventricular (LV) diastolic dysfunction has been known to occur early in all cardiovascular diseases and is also related to cardiovascular mortality.[1 2]"
Was change to..
"Left ventricular (LV) diastolic dysfunction has been known to play an important role in development of heart failure and is also related to cardiovascular mortality.[1 2]"

In **Reference** section,
"1. Leite-Moreira AF. Current perspectives in diastolic dysfunction and diastolic heart failure. *Heart* 2006;92(5):712-8. doi: 10.1136/hrt.2005.062950"
Was deleted, and added other reference as below,
"1. Kuznetsova T, Thijs L, Knez J, et al. Prognostic value of left ventricular diastolic dysfunction in a general population. *J Am Heart Assoc* 2014;3(3):e000789. doi: 10.1161/JAHA.114.000789"

[Comment #2]
The lack of women with parity data is substantially greater than 20%, which is one indication of a "poor quality" dataset.

[Response]
Thank you for your attentive comments. The KoRean wOmen'S chest pain rEgistry (KoROSE) consists of patients who visited with chest pain from 29 cardiac centers. Since the registry was created by recruiting patients from multi-centers, we feel unfortunate that we have not been able to provide the detailed information about obstetrics of all the patients in the registry. Once again thank your sophisticated comments.

[Comment #3]
3. Do not repeat data in Tables or Figures in the text.

[Response]
Thank you for your comments. As your comments, we deleted the repeated data in Tables or Figures in the manuscript as below.

In '**Baseline characteristics'** of **Result**s section,
"Waist circumference was significantly higher in the multiparity than in the low-parity group (79.6 ± 15.8 cm vs. 75.4 ± 16.3 cm, respectively; p = 0.001). The proportions of multiparity patients with diabetes mellitus and hypertension were larger than the proportions of low-parity patients (diabetes: 27.1% vs. 18.8%, respectively; p = 0.009; hypertension: 61.2% vs. 48.2%, respectively; p< 0.001). The proportion of multiparity patients with coronary artery disease was higher than that of the low-parity patients (65.5% vs. 47.3%, respectively; p< 0.001). The mean hemoglobin values were significantly lower in the multiparity patients than in the low-parity patients (12.5 ± 1.5 g/dL vs. 13.2 ± 7.8, g/dL, respectively; p = 0.029)."
Was changed to..
"Waist circumference was significantly higher in the multiparity than in the low-parity group. The proportions of multiparity patients with diabetes mellitus and hypertension were larger than the proportions of low-parity patients. The proportion of multiparity patients with coronary artery disease was also higher than that of the low-parity. The mean hemoglobin values were significantly lower and the NT-proBNP values were significantly higher in the multiparity patients than in the low-parity patients."

And, in '**Parity difference in LV diastolic dysfunction'** of **Results** section,

"The parameters representative for LV diastolic dysfunction showed significantly worse values for the multiparity patients than the parameters of the low-parity patients as follows: the multiparity patients showed a significantly lower MV E velocity, E/A ratio, and septal e´ velocity (E: 65.7 ± 20.0 cm/s vs. 69.1 ± 20.1 cm/s, respectively; p = 0.028; E/A ratio; 0.9 ± 0.7 vs. 1.0 ± 0.4, respectively; p = 0.037; e´septal; 5.5 ± 1.9 cm/s vs. 6.7 ± 2.4 cm/s, respectively; p< 0.001) and significantly higher E/e´ ratio and RVSP (E/e´ ratio; 13.1 ± 6.4 vs. 11.4 ± 5.3, respectively; p< 0.001; RVSP: 33.0 ± 9.9 vs. 29.9 ± 8.5 mm Hg, respectively; p< 0.001) than the low-parity patients."
Was revised to,
"The parameters representative for LV diastolic dysfunction showed significantly worse values for the multiparity patients than the parameters of the low-parity patients as follows: the multiparity patients showed a significantly lower MV E velocity, E/A ratio, and septal e´ velocity and significantly higher E/e´ ratio and RVSP than the low-parity patients."

And, in '**Multiparity as a predictor of LV diastolic dysfunction'** of **Results** section,

"ROC curve analysis identified a parity of 2.5 as the cutoff value for predicting LV diastolic dysfunction in multiparity patients (area under the curve, 0.66; sensitivity, 74.1%; specificity, 52.0%; 95% confidential interval (CI) 0.607-0.706; p< 0.001) (Figure 2)."
Was revised to,
"ROC curve analysis identified a parity of 2.5 as the cutoff value for predicting LV diastolic dysfunction in multiparity patients (Figure 2)."

[Comment #4]

Parity is typically confounded by education and socio-economic status, e.g. higher parity is associated with lower education and SES. This needs to be added to the analyses or reported as a major limitation.

[Response]
Thank you for your thoughtful comment. We agree with the reviewer's comment. Socioeconomic status and lower education are associated with higher parity and can also affect lifestyle behaviors and risk of cardiovascular disease. Unfortunately, there were no information about the socioeconomic status or education status in our registry. Therefore, we described the limitation about that in Discussion sections as following.

We added the sentences in the study limitation of **Discussion** section,
"Finally, though socioeconomic status and lower education are associated with higher parity and which can also affect lifestyle behaviors and risk of cardiovascular disease, we could not analyze the differences of the socioeconomic status and education status between multiparity and low-parity groups because of insufficient data about that."

[Comment 5]
Parity and CVD is controversial in the literature with lower CVD rates being observed in 1-4 births compared to higher rates for 0 and above 4. This needs to be analyzed and appropriate prior work cited Lv 2015, Catov 2008.

[Response]
We appreciate the reviewer's point and thank you for your thoughtful comment. We reviewed carefully those two articles according to your comment. Lv H. et al (2015) suggested that the number of parity and cardiovascular mortality have non-linear J-shaped relationship. They found that ever parity is inversely related to cardiovascular mortality until the parity number reaches 4 births. After 4 births, the linear relationship appeared to rebound. On the contrary, Catov JM. et al (2008) demonstrated that parous women had higher risk of cardiovascular disease than nulliparous women, and parity number 5 or more births had highest prevalence of cardiovascular disease. The outcome of our study was prevalence of LV diastolic dysfunction, and may differ from the results of cardiovascular disease or cardiovascular mortality in those previous studies. The prevalence of LV diastolic dysfunction increased according to parity number in our study. Therefore, we added the several sentences and cited those two articles as following.

Added sentences in '**LV diastolic dysfunction and multiparity'** of **Discussion** section,
"Lv H et al. suggested that the parity number is inversely associated with cardiovascular mortality until the parity number reaches 4 births.[17] After 4 births, the linear relationship appeared to rebound. On the contrary, Catov JM et al. demonstrated that parous women had higher risk of cardiovascular disease than nulliparous women, and parity number 5 or more birth had highest cardiovascular prevalence of cardiovascular disease.[18] The outcome of our study was prevalence of LV diastolic dysfunction only, and may differ from the results of cardiovascular disease or cardiovascular mortality in those previous studies."

And added references in **Reference** section,
17. Lv H, Wu H, Yin J, et al. Parity and Cardiovascular Disease Mortality: a Dose-Response Meta-Analysis of Cohort Studies. *Sci Rep* 2015;5:13411. doi: 10.1038/srep13411
18. Catov JM, Newman AB, Sutton-Tyrrell K, et al. Parity and cardiovascular disease risk among older women: how do pregnancy complications mediate the association? *Ann Epidemiol* 2008;18(12):873-9. doi: 10.1016/j.annepidem.2008.09.009

FORMATTING AMENDMENTS (if any)
[Comment #1]
Patient and Public Involvement:
We have implemented an additional requirement to all articles to include 'Patient and Public Involvement' statement within the main text of your main document. Please refer below for more information regarding this new instruction:
Authors must include a statement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'.

This should provide a brief response to the following questions:
How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences?
How did you involve patients in the design of this study?
Were patients involved in the recruitment to and conduct of the study?
How will the results be disseminated to study participants?
For randomised controlled trials, was the burden of the intervention assessed by patients themselves?
Patient advisers should also be thanked in the contributorship statement/acknowledgements.
If patients and or public were not involved please state this.

[Response]
Thank you for your valuable comment. Editor also request a statement about patient involvement in the methods section of the manuscript under the sub-heading 'Patient and Public Involvement'. We added "Patient and Public Involvement" as a sub-heading in the methods section. In our study, the development of research questions and outcome measures did not involve the patient's priorities, experience and preferences. Patients did not also involve in the design of the study and the recruitment to and conduct of the study. And, we did not disseminate the results to the study participants. Therefore, we mentioned a brief description about that as following sentences in methods section.

"Patient and Public Involvement
This study was conducted without patient and public involvement. The patients were not invited to comment on the study design and were not consulted to develop outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy."

[Comment #2]
Please re-upload your supplementary files in PDF format.

[Response]
Thank you for your comment. We made a supplementary file in PDF format and re-uploaded it.

[Comment #3]
Please include Figure legends at the end of your main manuscript.

[Response]
Thank you for your comment. We modified the position of figure legend to the end of our main manuscript.

[Comment #4]
Please provide better qualities figures, ensuring the figures are not pixelated when zoomed in on. Figures can be supplied in TIFF or JPG format (figures in PDF, DOCUMENT, EXCEL or POWERPOINT format will not be accepted), we also request that they have a resolution of at least 300 dpi and 90mm x 90mm of width.

[Response]
Thank you for your comment. We re-uploaded the figures with high resolution.

[Comment #5]
Upon checking your manuscript files, you've already uploaded the same figure embedded on your main document. Kindly delete the same figures embedded on your main document. Please note that we don't accept figures embedded on main document file.

[Response]
Thank you for your kind comment. We deleted the same figures embedded on our main document. We re-uploaded the figures with high resolution.

VERSION 2 – REVIEW

REVIEWER	Muhammed Keskin Sultan Abdülhamid Han Eğitim Ve Araştırma Hastanesi
REVIEW RETURNED	27-Oct-2018

GENERAL COMMENTS	I can see that the authors made a big effort to improve the manuscript after the reviewers' suggestions. The latest form of the manuscript is quite publishable.