

## Appendix 1. Participating Institutions and Researchers

The following institutions and researchers conducted the Sleep Disordered Breathing Study within the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-be (nuMoM2b) Network: **National Heart Lung and Blood Institute** - Aaron Laposky, PhD; **Eunice Kennedy Shriver National Institute of Child Health and Human Development** - Uma M. Reddy, MD, MPH, Marian Willinger, PhD, Maurice Davis, DHA, MPA, MHSA; N, PhD; **Case Western Reserve University / Ohio State University** - Brian M. Mercer, MD, Jay Iams, MD, Wendy Dalton, RN, Cheryl Latimer, RN, LuAnn Polito, RN, JD, Judette M. Louis, MD; **Columbia University / Christiana Care** - Matthew K. Hoffman, MD, MPH, Ronald Wapner, MD, Karin Fuchs, MD, Caroline Torres, MD, Stephanie Lynch, RN, BSN, CCRC, Ameneh Onativia, MD, Michelle DiVito, MSN, CCRC. Chia-Ling, Nhan-Chang, MD, Robert C. Basner, MD ; **Indiana University** - David M. Haas, MD, MS, Tatiana Foroud, PhD, Emily Perkins, BS, MA, CCRP, Shannon Barnes, RN, MSN, Alicia Winters, BS, Catherine L. McCormick, RN, Frank P. Schubert, MD, MS ; **University of Pittsburgh** - Hyagriv N. Simhan, MD, MSCR, Steve N. Caritis, MD, Melissa Bickus, R.N., B.S., Paul D. Speer, MD, Stephen P. Emery, MD, Ashi R. Daftary, MD, Francesca L. Facco, MD; **Northwestern University** - William A. Grobman, MD, MBA, Alan M. Peaceman, MD, Phyllis C. Zee, MD, PhD , Peggy Campbell, RN, BSN, CCRC, Jessica S. Shepard, MPH , Crystal N. Williams, BA; **University of California at Irvine** - Deborah A. Wing, MD, Pathikd D. Wadhwa, MD, PhD, Michael P. Nageotte, MD, Judith H. Chung, MD, PhD, Pamela J. Rumney, RNC, CCRC, Manuel Porto, MD, Valerie Pham, RDMS; **University of Pennsylvania** - Samuel Parry, MD, Jack Ludmir, MD, Michal Elovitz, MD, Mary Peters, BA, MPH, Brittany Araujo, BS, Grace Pien, MD, MSCE; **University of Utah** - Robert M. Silver, M.D., M. Sean Esplin, MD, Kelly Vorwaller, RN, Julie Postma, RN, Valerie Morby, RN, Melanie Williams, RN, Linda Meadows, RN; **RTI International** - Corette B. Parker, DrPH, Matthew A. Koch, MD, PhD, Deborah W. McFadden, MBA, Barbara V. Alexander, MSPH, Venkat Yetukuri, MS, Shannon Hunter, MS, Tommy E. Holder, Jr, BS, Holly L. Franklin, MPH, Martha J. DeCain, BS, Christopher Griggs, BS; **Harvard University, Brigham and Women's Hospital** - Susan Redline, MD, MPH, Daniel Mobley, RPSGT, Susan Surovec, BA, Julianne Ulanski, BS ; **University of Texas Medical Branch at Galveston** - George R. Saade, MD.

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The authors provided this information as a supplement to their article.

## Appendix 2. nuMoM2b Study Definitions of Hypertensive Disorders of Pregnancy

This appendix provides nuMoM2b study definitions of hypertensive disorders of pregnancy. The study pre-dates the American Congress of Obstetricians and Gynecologists 2013 guidelines monograph found at: <http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy>

Exhibit 2.1 shows nuMoM2b definitions of hypertension and proteinuria at baseline (prior to pregnancy or prior to 20<sup>0</sup> weeks gestation).

Exhibit 2.2 gives definitions of HELLP syndrome and eclampsia, which are new onset hypertensive disorders (occurring at or after 20<sup>0</sup> weeks gestation). These definitions are applicable to all participants irrespective of baseline group (chronic hypertension, baseline proteinuria, both, neither).

Exhibit 2.3 provides a table of definitions of gestational hypertension, mild preeclampsia, severe preeclampsia, and superimposed preeclampsia, according to baseline group. Shown are the baseline groups, applicable diagnoses, and nuMoM2b clinical criteria (at or after 20<sup>0</sup> weeks of gestation through 14 days postpartum) for these new onset maternal hypertensive disorders. In Section A, the occurrence of new onset hypertension (Section A.1) plus one or more of the criteria marked with an 'X' in Section A.2 establishes the diagnosis of preeclampsia. Given a diagnosis of preeclampsia, the occurrence of any criterion marked with an 'S' establishes the preeclampsia as severe; otherwise the diagnosis is mild preeclampsia. Note that some criteria, denoted with 'X, S' have a dual role as indicators of preeclampsia and of severe preeclampsia given a diagnosis of preeclampsia.

Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure

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## Exhibit 2.1 – Baseline hypertension and proteinuria

**Chronic hypertension (CHTN)** – (1) a diagnosis of hypertension prior to pregnancy or (2) hypertension (systolic  $\geq 140$  mmHg OR diastolic  $\geq 90$  mmHg on two occasions at least 6 hours apart or on one occasion followed by antihypertensive medication therapy) documented prior to pregnancy or prior to 20<sup>0</sup> weeks gestation.

**Baseline proteinuria  $\geq 300$  mg/ 24hr** – total protein  $\geq 300$  mg in a 24-hour urine collection documented prior to pregnancy or prior to 20<sup>0</sup> weeks gestation.

## Exhibit 2.2 – New-onset hypertensive disorders (occurring at or after 20<sup>0</sup> weeks of gestation through 14 days postpartum) applicable to all participants irrespective of baseline status regarding chronic hypertension (CHTN) and proteinuria

**HELLP syndrome** – the occurrence of all of the following criteria:

- a. Hemolysis – evidenced by (1) serum total bilirubin  $\geq 1.2$  mg/dL (20  $\mu\text{mol/L}$ ), (2) serum lactate dehydrogenase (LDH)  $\geq 600$  IU/L, or (3) hemolysis on peripheral smear
- b. Thrombocytopenia (platelet count  $< 100,000$  /mm<sup>3</sup>)
- c. Serum aspartate aminotransferase (AST)  $\geq 100$  IU/L

**Eclampsia** – the occurrence of a seizure without another known cause.

## Exhibit 2.3 – nuMoM2b definitions for new onset hypertensive disorders, by baseline status regarding chronic hypertension (CHTN) and proteinuria

**Baseline groups, applicable diagnoses, and nuMoM2b clinical criteria (at or after 20<sup>0</sup> weeks of gestation through 14 days postpartum) for new onset maternal hypertensive disorders**

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### A. Participants without CHTN or baseline proteinuria $\geq 300$ mg/ 24hr

#### 1. Gestational hypertension – the occurrence of new onset hypertension, defined as:

- a. SBP  $\geq 140$  or DBP  $\geq 90$  on 2 occasions  $\geq 6$ hr apart or 1 occasion with subsequent antihypertensive therapy, excluding blood pressures recorded during the second stage of labor

#### 2. Preeclampsia – the occurrence of (1) new onset hypertension plus one or more criteria marked with an "X" below, or (2) HELLP syndrome

**Severe preeclampsia** – (1) a diagnosis of preeclampsia plus one or more criteria marked with an "S" below, or (2) HELLP syndrome

**Mild preeclampsia** – a diagnosis of preeclampsia that does not meet criteria for severe preeclampsia

- |    |  |      |
|----|--|------|
| a. | Proteinuria $\geq 300$ mg/ 24hr; or, if no 24-hour urine protein available, protein/creatinine ratio $\geq 0.3$ or dipstick $\geq 2+$  | X    |
| b. | Thrombocytopenia (platelet count $< 100,000$ /mm <sup>3</sup> )  | X, S |
| c. | Pulmonary edema  | X, S |
| d. | Severe hypertension: SBP $\geq 160$ or DBP $\geq 110$ on 2 occasions $\geq 6$ hr apart or 1 occasion with subsequent antihypertensive therapy, excluding blood pressures recorded during the second stage of labor | S    |
| e. | Proteinuria $\geq 5,000$ mg/ 24hr  | S    |
| f. | Oliguria (urine output $< 500$ mL/ 24hr)   | S    |

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- |    |  |   |
|----|--|---|
| g. | Severe headache  | S |
| h. | Epigastric pain  | S |
| i. | Fetal growth restriction (antenatal diagnosis; operationalized as estimated fetal weight $\leq$ 10th percentile for gestational age by ultrasound examination) | S |

**Exhibit 2.3 (cont.) – nuMoM2b a definitions for new onset hypertensive disorders, by baseline status regarding chronic hypertension (CHTN) and proteinuria**

**Baseline groups, applicable diagnoses, and nuMoM2b clinical criteria (at or after 20<sup>0</sup> weeks of gestation through 14 days postpartum) for new onset maternal hypertensive disorders**

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**B. Participants with baseline proteinuria  $\geq$ 300 mg/ 24hr only**

**1. Gestational hypertension – the occurrence of new onset hypertension, defined as:**

- a. SBP  $\geq$ 140 or DBP  $\geq$ 90 on 2 occasions  $\geq$ 6hr apart or 1 occasion with subsequent antihypertensive therapy, excluding blood pressures recorded during the second stage of labor

**2. Superimposed preeclampsia – the occurrence of one or more of the following:**

- a. Sudden increase in proteinuria (5 times the baseline value, or 2 times a baseline value of  $\geq$ 5,000 mg/ 24hr)
- b. Thrombocytopenia (platelet count  $<$ 100,000 /mm<sup>3</sup>)
- c. Serum aspartate aminotransferase (AST)  $\geq$ 100 IU/L
- d. Severe headache
- e. Epigastric pain

NOTE: the occurrence of HELLP satisfies superimposed preeclampsia criteria B.2.b and B.2.c

**C. Participants with CHTN only**

**1. Superimposed preeclampsia – the occurrence of one or more of the following:**

- a. Proteinuria  $\geq$ 300 mg/ 24hr; or, if no 24-hour urine protein available, protein/creatinine ratio  $\geq$ 0.3 or dipstick  $\geq$ 2+
- b. Thrombocytopenia (platelet count  $<$ 100,000 /mm<sup>3</sup>)

NOTE: the occurrence of HELLP satisfies superimposed preeclampsia criterion C.1.b

**D. Participants with CHTN and baseline proteinuria  $\geq$ 300 mg/ 24hr**

**1. Superimposed preeclampsia – the occurrence of one or more of the following:**

- a. Worsening hypertension, as shown by two diastolic blood pressures  $\geq$ 110 mm Hg taken four hours apart in the week before delivery, excluding blood pressures recorded during the second stage of labor; AND any of these findings:
  - i. Sudden increase in proteinuria (5 times the baseline value, or 2 times a baseline value of  $\geq$ 5,000 mg/ 24hr)
  - ii. Severe headache

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- iii. Epigastric pain
- b. Thrombocytopenia (platelet count  $<100,000 /\text{mm}^3$ )
- c. Serum aspartate aminotransferase (AST)  $\geq 100$  IU/L

NOTE: the occurrence of HELLP satisfies superimposed preeclampsia criteria D.1.b and D.1.c

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**Appendix 3. Baseline Characteristics for nuMoM2b Cohort Participants and SDB Subcohort Participants**

Baseline Characteristics	Cohorts		p-value*
	nuMoM2b (N = 10,038)	SDB (N = 3,705)	
Maternal age, in years			
Mean ± standard deviation	26.9 ± 5.7	26.7 ± 5.6	<0.001
Category: n (%)			0.68
13-21	2,133 (21.3)	803 (21.7)	
22-35	7,222 (72.0)	2,660 (71.8)	
>35	673 (6.7)	242 (6.5)	
Maternal race: n (%)			0.26
White Non-Hispanic	5,989 (59.7)	2,209 (59.6)	
Black Non-Hispanic	1,418 (14.1)	524 (14.1)	
Hispanic	1,700 (17.0)	655 (17.7)	
Asian	407 (4.1)	133 (3.6)	
Other	514 (5.1)	184 (5.0)	
Body mass index, in kg/m <sup>2</sup>			
Mean ± standard deviation	26.4 ± 6.4	26.5 ± 6.4	0.12
Category: n (%)			0.17
<25	5,193 (52.9)	1,891 (51.7)	
25 to <30	2,445 (24.9)	927 (25.3)	
≥30	2,181 (22.2)	840 (23.9)	
Smoked during 3 months prior to pregnancy: n (%)	1,782 (17.8)	671 (18.1)	0.51
Chronic hypertension: n (%)	243 (2.6)	84 (2.4)	0.33
Pre-gestational diabetes: n (%)	151 (1.6)	56 (1.6)	0.91
Neck circumference, in cm			
Mean ± standard deviation	32.9 ± 3.0	33.0 ± 3.0	0.07
Category: n (%)			0.02
<34	5,797 (67.9)	2,340 (66.3)	

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34 to 36.5	1,804 (21.1)	797 (22.6)	
>36.5	936 (11.0)	392 (11.1)	

Abbreviations: nuMoM2b=Nulliparous Pregnancy Outcome Study: Monitoring Mothers-to-be; SDB=Sleep Disordered Breathing Substudy; kg/m<sup>2</sup>=kilograms per square meters; cm=centimeters

\* p-values are shown for chi-square tests for participation (nuMoM2b only versus nuMoM2b and SDB) and the categorical baseline characteristics and from ANOVA F-tests for participation and continuous baseline characteristics

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**Appendix 4. Elements of the Apnea Hypopnea Index, AHI, in Early and Mid- Pregnancy Sleep Disordered Breathing\***

Characteristic	N	Mean ± SD	Min	Percentiles					Max
				10th	25th	50th	75th	90th	
Early Pregnancy, AHI≥5									
<b>Percent of AHI due to:</b>									
Hypopnea	114	91.3 ±18.5	1.4	70.7	92.7	99.4	100.0	100.0	100.0
Central Apnea	114	2.0 ±9.7	0.0	0.0	0.0	0.0	0.0	2.4	94.5
Obstructive Apnea	114	6.7 ±15.8	0.0	0.0	0.0	0.0	5.1	22.2	97.7
<b>Percent of Apnea:</b>									
Obstructive	58	78.7 ±32.4	0.0	14.3	66.7	100.0	100.0	100.0	100.0
Mid Pregnancy, AHI≥5									
<b>Percent of AHI due to:</b>									
Hypopnea	206	93.1 ±13.6	17.4	79.2	93.0	98.5	100.0	100.0	100.0
Central Apnea	206	1.1 ±5.1	0.0	0.0	0.0	0.0	0.0	2.3	59.5
Obstructive Apnea	206	5.8 ±12.7	0.0	0.0	0.0	0.0	5.8	18.2	81.1
<b>Percent of Apnea:</b>									
Obstructive	114	79.1 ±37.8	0.0	0.0	83.3	100.0	100.0	100.0	100.0

Abbreviations: AHI=apnea hypopnea index; SD=standard deviation.

\* For each participant with an AHI≥5, variables were constructed for the percent of the AHI due to hypopnea, percent due to central apnea, and percent due to obstructive apnea. Also, among the women with apnea and an AHI≥5, the percent of the apnea events that were obstructive is computed. The mean ± SD and percentiles are presented for these four variable in early and mid- pregnancy.

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**Appendix 5. Baseline Characteristics of Participants Completing the Mid-Pregnancy Sleep Study According to the Apnea Hypopnea Index, AHI, in Mid Pregnancy**

Baseline Characteristics	Failed Study* (N = 348)	All Apneas and Hypopneas with ≥3% Oxygen Desaturation / Hour				p-value†
		AHI=0 (N = 348)	0<AHI<5 (N = 1,920)	5≤AHI<15 (N = 177)	AHI≥15 (N = 29)	
Maternal age, in years						
Mean ± standard deviation	26.2 ± 5.8	25.9 ± 5.0	26.9 ± 5.4	29.6 ± 5.5	31.4 ± 5.5	<.001
Category: n (%)						<.001
13-21	90 (25.9)	87 (25.0)	354 (18.4)	12 (6.8)	1 (3.4)	
22-35	235 (67.5)	254 (73.0)	1,446 (75.3)	140 (79.1)	21 (72.4)	
>35	23 (6.6)	7 (2.0)	120 (6.3)	25 (14.1)	7 (24.1)	
Maternal race: n (%)						0.06
White Non-Hispanic	199 (57.2)	216 (62.1)	1,230 (64.1)	108 (61.0)	16 (55.2)	
Black Non-Hispanic	69 (19.8)	36 (10.3)	213 (11.1)	26 (14.7)	6 (20.7)	
Hispanic	56 (16.1)	67 (19.3)	324 (16.9)	20 (11.3)	5 (17.2)	
Asian	7 (2.0)	10 (2.9)	66 (3.4)	13 (7.3)	1 (3.4)	
Other	17 (4.9)	19 (5.5)	87 (4.5)	10 (5.6)	1 (3.4)	
Body mass index, in kg/m <sup>2</sup>						
Mean ± standard deviation	26.9 ± 6.7	23.2 ± 4.4	26.4 ± 6.2	33.0 ± 8.0	36.9 ± 8.7	<.001
Category: n (%)						<.001
<25	170 (49.1)	260 (76.5)	996 (52.4)	28 (16.0)	0 (0.0)	
25 to <30	91 (26.3)	55 (16.2)	489 (25.7)	37 (21.1)	4 (13.8)	
≥30	85 (24.6)	25 (7.4)	416 (21.9)	110 (62.9)	25 (86.2)	
Smoked during 3 months prior to pregnancy: n (%)	83 (23.9)	48 (13.8)	312 (16.3)	44 (24.9)	4 (13.8)	0.01
Chronic hypertension: n (%)	10 (2.9)	3 (0.9)	36 (1.9)	15 (8.5)	3 (10.3)	<.001
Pre-gestational diabetes: n (%)	6 (1.7)	32 (1.7)	3 (1.7)	1 (3.4)	0 (0.0)	0.05
Neck circumference, in cm						
Mean ± standard deviation	33.1 ± 2.9	31.7 ± 2.2	32.8 ± 2.8	35.2 ± 3.9	37.6 ± 3.8	<.001
Category: n (%)						<.001
<34	219 (65.6)	292 (87.4)	1,252 (67.5)	57 (33.3)	5 (17.9)	
34 to 36.5	80 (24.0)	33 (9.9)	426 (23.0)	65 (38.0)	8 (28.6)	

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>36.5	35 (10.5)	9 (2.7)	176 (9.5)	49 (28.7)	15 (53.6)	
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Abbreviations: AHI=apnea hypopnea index; kg/m<sup>2</sup>=kilograms per square meters; cm=centimeters

\* Tests comparing baseline characteristics of women with failed studies versus those with adequate data found significant differences at p<0.05 for: age (continuous and categorical), race, and smoking status.

† P-values are shown for chi-square tests for AHI (apnea hypopnea index) and the categorical baseline characteristics and from ANOVA F-tests for AHI and continuous baseline characteristics. Due to the small number of women with AHI≥15, the 5≤AHI<15 and AHI≥15 categories were combined for these tests.

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**Appendix 6. Crude and Adjusted\* Odds Ratios for Preeclampsia† According to Apnea Hypopnea Index in Mid-pregnancy Excluding Adjustment for Weight Gain**

All Apneas and Hypopneas with 3% Oxygen Desaturation / hour	n/N (%)	Crude Odds Ratios		Adjusted Odds Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Mid-pregnancy (N=2,472)					
AHI<5 (referent)	114/2266 (5.0)	1.00	<.001	1.00	0.009
AHI≥5	26/206 (12.6)	2.73 (1.73-4.29)		1.95 (1.18-3.23)	
AHI=0 (referent)	15/347 (4.3)	1.00	<0.001	1.00	0.07
0<AHI<5	99/1919 (5.2)	1.20 (0.69-2.10)		1.03 (0.58-1.82)	
5≤AHI<15	21/177 (11.9)	2.98 (1.50-5.94)		1.91 (0.90-4.06)	
AHI≥15	5/29 (17.2)	4.61 (1.54-13.76)		2.64 (0.81-8.55)	

Abbreviations: AHI=apnea hypopnea index; 95% CI=95% confidence interval; BMI=body mass index

\* Adjusted for maternal age (≤21, 22-35, and >35), BMI (<25, 25 to <30, ≥30) and chronic hypertension (yes, no) as determined in early pregnancy. The adjusted analyses included N<sub>m</sub>=2,441 observations.

†Preeclampsia includes mild, severe, and superimposed preeclampsia and eclampsia.

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**Appendix 7. Crude and Adjusted\* Odds Ratios for Gestational Diabetes For Women without Pre-gestational Diabetes According to Apnea Hypopnea Index in Mid-pregnancy Excluding Adjustment for Weight Gain**

All Apneas and Hypopneas with 3% Oxygen Desaturation / hour	n/N (%)	Crude Odds Ratios		Adjusted Odds Ratios	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Mid-pregnancy (N=2,432)					
AHI<5 (referent)	69/2231 (3.1)	1.00	<.001	1.00	<0.001
AHI≥5	27/201 (13.4)	4.86 (3.04-7.79)		2.81 (1.64-4.81)	
AHI=0 (referent)	2/347 (0.6)	1.00	<.001	1.00	<0.001
0<AHI<5	67/1884 (3.6)	6.36 (1.55-26.07)		4.92 (1.19-20.34)	
5≤AHI<15	22/173 (12.7)	25.12 (5.84-108.17)		12.83 (2.85-57.68)	
AHI≥15	5/28 (17.9)	37.49 (6.90-203.79)		14.44 (2.47-84.58)	

Abbreviations: AHI=apnea hypopnea index; 95% CI=95% confidence interval; BMI=body mass index

\* Adjusted for maternal age (≤21, 22-35, and >35), BMI (<25, 25 to <30, ≥30) and chronic hypertension (yes, no) as determined in early pregnancy. The adjusted analyses included N<sub>m</sub>=2,401 observations.

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