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Impact of Maternal Obesity on Neonatal Heart Rate and Cardiac Size

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AMG, AP, MCV, DP, ADE, PJC LP, and PDT contributed to study design. AP, TRW, SJ, YY, EEB, PTS, KWDS, JC, SS, FM, AB, CS were involved in data collection and analysis. All authors were involved in writing and reviewing the manuscript.

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Informed Consent

Written informed parental consent was obtained in all cases.

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Abstract

Background: Maternal obesity may increase offspring risk of cardiovascular disease. We assessed the impact of maternal obesity on cardiac structure and function in newborns as a marker of fetal cardiac growth.

Methods: Neonates born to mothers of healthy weight (BMI 20-25kg/m^2, n=56) and to mothers who were obese (BMI≥30kg/m^2, n=31) underwent 25-minute continuous electrocardiogram recording and non-sedated, free-breathing cardiac magnetic resonance imaging within 72 hours of birth.

Results: Mean (SD) heart rate during sleep was higher in infants born to mothers who were vs were not obese (123(12.6) *vs* 114(9.8) beats/min, p=0.002). Heart rate variability during sleep was lower in infants born to mothers who were vs were not obese (standard deviation of normal-to-normal R-R interval (SDNN) 34.6(16.8) *vs* 43.9(16.5) milliseconds, p=0.05). Similar heart rate changes were seen during wakefulness. Left ventricular end-diastolic volume (2.35(0.14) *vs* 2.54(0.29) ml/kg, p=0.03) and stroke volume 1.50(0.09) *vs* 1.60(0.14), p=0.04) were decreased in infants born to mothers who were vs were not obese. There were no differences in left ventricular end-systolic volume, ejection fraction, output or myocardial mass between the groups.

Conclusion: Maternal obesity was associated with increased heart rate, decreased heart rate variability and decreased left ventricular volumes in newborns. If persistent these changes may provide a causal mechanism for the increased cardiovascular risk in adult offspring of mothers with obesity. In turn, modifying antenatal and perinatal maternal health may have the potential to optimize long term cardiovascular health in offspring.

Introduction

The association between the intra-uterine environment and long-term cardiovascular and metabolic outcomes in offspring is well-established(1). The 'Developmental Origins of Health and Disease' hypothesis now encompasses multiple aspects of the intrauterine environment and maternal wellbeing, including body mass index (BMI)(2). In England 22.1% of women attending their first antenatal visit are currently clinically obese(3). Maternal obesity is a risk factor for multiple complications for both mother and fetus. It is increasingly recognized that maternal obesity has consequences for offspring health later in life, including insulin resistance, obesity, hypertension(4-6) cardiovascular disease(7, 8), cardiovascular mortality and all-cause mortality(9).

While there is some data on the impact of maternal obesity on fetal cardiac function(10, 11) little is known about the impact of maternal obesity on fetal cardiac growth. Cardiac Magnetic Resonance (CMR) imaging techniques provide gold standard quantification of cardiac volume and myocardial mass in adults(12). CMR techniques have now been optimized for assessment of neonatal cardiac size(13, 14). The goal of this study was to assess the impact of maternal obesity on heart rate, heart rate variability and cardiac size in newborns.

Methods

Cohort

The cohort studied were infants born to women receiving care at St Thomas' Hospital, Guy's and St. Thomas' NHS Foundation Trust (GSTFT), London, UK. Shortly after delivery, women with an early pregnancy BMI$\geqq$30kg/m^2 (as assessed by the health care provider in the 1st trimester)

were invited to consent for their newborn infants. The women approached were either from the standard care arm of the UK Pregnancies Better Eating and Activity Trial (UPBEAT, ISRCTN89971375)(15), or women who had been identified as eligible from their first trimester BMI. For the control group of infants (n=56), we approached women identified as having an early pregnancy BMI of 20-25 kg/m^2.

Women were not eligible if they had a multiple pregnancy, a pre-existing medical history (hypertension, diabetes, renal disease, lupus and antiphospholipid syndrome), or if their infants had a confirmed congenital abnormality, abnormal fetal karyotype, depressed Apgar scores at birth or neonatal intensive care admission. Women in the control group were not eligible if they had gestational diabetes in the index pregnancy.

The study design and protocol were approved by the NHS Research Ethics Committee (UK Integrated Research Application System; reference 13/LO/1108). All assessments were performed for research purposes only, written informed parental consent was obtained in all cases.

Heart Rate and Heart Rate Variability

A 25-minute, continuous electrocardiogram (ECG) recording was measured in swaddled neonates within 72 hours of delivery. Time of the last feed and sleep state of the neonate throughout the ECG recording were documented. The ECG recording was performed using the Medilog AR12 Plus HRV High Performance Recorder and analyzed using the Medilog Darwin

V2 software. HR and HRV of the ECG were analyzed according to sleep state of the neonate. Analysis of the ECG was performed blind to maternal BMI.

Cardiac MRI Acquisition

Newborns underwent non-sedated CMR within 72 hours of delivery using a feed-and-wrap technique on a Philips 3-Tesla MR Achieva scanner with an 8-channel receive coil. Steady-state free-precession (SSFP) cine sequences were acquired to localize cardiac anatomy, before acquisition of an optimized, retrospectively-gated 2D SSFP 10-slice short axis cine stack with patient-specific shimming as previously described(11). SSFP parameters were: in-plane resolution 1x1 mm; 20 phases/cycle, slice thickness 4 mm; repetition time 3.8ms; echo time 1.9ms; flip angle 35°; four signal averages. Varied negative inter-slice gap depending on cardiac base-to-apex length enabled interpolation of slice thickness to <4 mm whilst ensuring full coverage of both ventricles in all infants. No CMR-acceleration methods or respiratory gating techniques were used; acquisition time was 4-6 minutes. Anonymized CMR data were stored on a protected digital archive for subsequent analysis.

Cardiac MRI Analysis

Stacks were segmented at end-diastole and end-systole according to standard CMR methodology(16). A trained pediatric cardiologist (JS) performed a detailed manual tracing of the epi- and endocardium (Figure 1) using Circle CV software. Contour position was subsequently confirmed by an independent second observer (KS). Both operators were blinded to maternal BMI. Chamber volumes were indexed to both infant weight (standard in neonatal practice), and body surface area by the Haycock Formula ($weight^{0.5378}$x$length^{0.3964}$x0.024265)

(standard in pediatric cardiology practice)(17). Myocardial mass was calculated by multiplying the myocardial volume by 1.05 g/ml. Reliability of quantification of left and right ventricular stroke volume was assessed by comparing left and right ventricular stroke volumes in individual infants, under the assumption that there were no significant persistent fetal shunt pathways such that left and right sided stroke volumes should be equal.

Statistical Analysis

Demographic data are presented as median and range. HR, HRV and cardiac size variables are presented as mean and standard deviation and were compared between groups by unpaired Student t test. Associations between continuous variables were assessed by simple linear regression. Consistency of left and right sided stroke volumes was made by median variability and Bland-Altman analysis of mean bias and limits of agreement(18). A probability value of <0.05 was considered significant.

Results

Cohort

ECG and MRI acquisitions were attempted in 82 and 39 infants respectively (Figure 2). Demographic data for the cohort are shown in table 1. In total, 6 women with obesity (first trimester BMI$\geq$30 kg/m^2) who participated in the standard-care arm of the UK Pregnancies Better Eating and Activity Trial (UPBEAT) were included, along with 25 women with obesity identified from antenatal records. Mean (SD) maternal BMI was 22.6 (1.8) kg/m^2 in the lean group, and 35.6 (4.1) kg/m^2 in the obese group (Table 1). Maternal household income was higher

in the lean group (p=0.015). There were no differences in maternal ethnicity, age, or infant gestational age at delivery, sex, mode of delivery, birth weight or body surface area between infants born to lean and obese women.

Heart Rate and Heart Rate Variability

In 17 cases ECG analysis showed movement artefacts/low validity preventing inclusion. In 2 further cases data were excluded prior to group analysis due to outlier status. ECG recordings of adequate quality for quantitative analysis were therefore obtained in 63 infants (Figure 2).

Asleep - Mean (SD) heart rate during sleep was higher in infants born to mothers who were obese (123 (12.6) vs 114 (9.8) beats/min, p=0.002). Mean (SD) of normal-to-normal R-R interval (SDNN) was lower in infants born to mothers who were obese (34.6 (16.8) vs 43.9 (16.5) milliseconds, p=0.05), (Table 2).

Awake - Mean (SD) heart rate during wakefulness was higher in infants born to mothers who were obese (134 (13) vs 125 (15) beats/min, p=0.04). Mean (SD) SDNN was lower in infants born to mothers who were obese (35.6 (14.0) vs 48.1 (18.3) milliseconds, p=0.017)(Table 2).

There were no differences in metrics of high, low and very low frequency variability in the frequency domain.

Cardiac MRI Assessment

Cardiac MR Imaging was attempted in 37 infants. In 4 infants the cardiac MR images were either incomplete or subject to significant image artefact. Cardiac MR images of adequate quality for quantitative analysis were therefore obtained in 33 infants(Figure 2).

Heart Rate During MRI

Mean heart rate assessed at the time of MRI was significantly increased in infants born to mothers who were obese (121 (13.9) vs 110 (9.6) beats/min, p=0.01, Table 3).

Left Ventricular Volume

Left ventricular end-diastolic volume was decreased in infants born to mothers with obesity (2.35 (0.14) vs 2.54 (0.29) ml/kg, p=0.03), as was left ventricular stroke volume (1.50 (0.09) vs 1.60 (0.14) ml/kg, p=0.04). There were no differences in left ventricular end-systolic volume, left ventricular ejection fraction or left ventricular output between the groups (Table 3). Significant differences in left ventricular end-diastolic volume and stroke volume continued to be present when measures were indexed to infant body surface area (Table 4).

Right Ventricular Volume

There were no significant differences in right ventricular end-diastolic volume, end-systolic volume, stroke volume, right ventricular ejection fraction or right ventricular output between the groups (Tables 3 and 4). However right ventricular end diastolic volume and right ventricular stroke volume tended to be lower in infants born to mothers with obesity.

Myocardial Mass

There were no differences in left or right ventricular myocardial mass between groups (Tables 3 and 4).

Validation of Volume Measures

Measures of left and right ventricular stroke volume in individual infants were highly correlated (R=0.72). Median variability between left and right ventricular stroke volume was 4.7%. Mean difference (95% limits of agreement) for measured left and right ventricular stroke volume was 0.03 (-0.20 - 0.26) ml/kg.

Discussion

In this cohort of newborns maternal obesity in early pregnancy was associated with increased heart rate, decreased heart rate variability and decreased left ventricular volume. Increases in heart rate were present during both sleep and wakefulness. Decreases in left ventricular volume were present when absolute measures were indexed to both weight and body surface area.

The increase in heart rate seen in infants born to obese mothers was not only statistically but also clinically significant, elevations of 9-11 beats/min during both sleep and wakefulness. In adulthood similar degrees of resting heart rate elevation are associated with increased risks of cardiovascular disease, cancer and all-cause mortality(19).

Our novel findings extend those of other groups studying the impact of maternal obesity on cardiac function in human fetuses. Voegtline employed actocardiography to demonstrate that fetuses of obese mothers had significantly reduced heart rate variability and a trend to a higher

heart rate(20). Mat Husin used magnetocardiogram techniques to overcome prior challenges in reliably assessing exact fetal heart rate and demonstrated that fetuses of obese women have decreased heart rate variability (21). In an animal model Guzzardi et al demonstrated an increase in heart rate in newborn minipigs born to sows fed a high fat diet; with increases in heart rate still present when the animals reached maturity(22). To our knowledge no previous study has reported an increase in heart rate in neonates born to obese women.

These alterations in fetal heart rate and heart rate variability may be representative of altered autonomic function. Heart rate and heart rate variability are driven by interactions between the sympathetic and parasympathetic nervous systems. The increased neonatal heart rate and decreased heart rate variability reported here suggest a shift in sympatho-vagal balance. It is well established that maternal heart rate is increased, and autonomic responsiveness is decreased in obese pregnant women(23). Animal models also demonstrate that maternal obesity drives a preponderance of sympathetic activity in offspring(24) which may reflect the observed association between maternal and fetal autonomic tone(25). While the mechanisms of altered autonomic function with obesity have not been elucidated, possibilities include a direct central effect of insulin on autonomic activity(26, 27) or impact of maternal and fetal leptin(28, 29).

To our knowledge this is the first application of cardiac MRI techniques to assessment of cardiac size in infants born to obese mothers. Cardiac MRI techniques are the gold standard for volumetric assessments in adults(12). Our group has systematically optimized cardiac MRI for use in the newborn population(13) and demonstrated high precision of the techniques(30, 31).

Excellent repeatability in quantification of stroke volumes is again shown here, with median variability of 4.7%, and 95% limits of agreement of 0.20-0.26ml/kg.

Reductions in chamber volume in the presence of maternal obesity were seen in the left ventricle when indexing for both weight and body surface area making it unlikely that differences were artefactual from indexing to altered body phenotypes. Similar trends were seen in the right ventricle. We also demonstrated a reduced stroke volume in the neonates of obese mothers. Since fetal heart growth is driven by flow volume(32) an increase in fetal heart rate from altered autonomic balance could conceivably trigger a reduction in chamber size, as a lower stroke volume is required to maintain the same total cardiac output. There were no differences in left or right myocardial mass between the groups.

Previously reported cohorts of infants born to obese mothers have not shown consistent data on cardiac size. Guzzardi et al showed increased left ventricular mass in human newborns, but no differences in end diastolic volume or stroke volume. However these authors utilized ultrasound (22) which has significantly lower accuracy compared to MRI in quantification of chamber volume and myocardial mass(33).

The clinical significance of our findings remains unknown. In adults increased heart rate and decreased heart rate variability are both associated with multiple adverse outcomes(19, 34). The Helsinki Birth Cohort Study demonstrated significant increases in offspring cardiovascular risk in the presence of maternal obesity(8). A recent population cohort study from Sweden has identified a strong relationship between maternal obesity and cardiovascular disease in 1-25yr olds(7) and another from Scotland reported an association between maternal obesity and all-

cause mortality in adult offspring, with offspring of obese women having a 29% increased risk of cardiovascular events in adulthood and premature death from cardiovascular events(9).

Alterations in heart rate and cardiac growth present a potentially modifiable mechanism for adverse outcomes in offspring of women with obesity. We have recently demonstrated that the life-style intervention during pregnancy in the UPBEAT trial was associated with a reduction in resting heart rate in children followed up at three years of age (n=403, HR 91 vs 96 beats/min, p=0.01)(35). Sympathetic overdrive, manifesting as tachycardia, is considered a primary driver of adult heart failure(36) and it is postulated that every single beat/minute increase in heart rate may increase the risk of death or hospitalization by up to 3%(36). Lower ventricular size may signify lower myocardial reserve which would then predispose to heart failure in the presence of ischemia or dysfunction.

This study is limited by its small sample size, especially for the MRI studies. However cardiac MRI in the newborn is expensive and technically challenging. Parental consent rates were around 30% overall, and lower for the CMR component. Not all findings are consistent between our study and others, such that impact of maternal obesity on heart rate, HRV, cardiac mass and chamber size all require further study. Further studies in larger cohorts are also required to examine the impact of potential confounders such as maternal blood pressure, glucose homeostasis, lipid profile, weight gain during pregnancy, antenatal steroid administration, etc. Lastly, we are unable to determine whether an increase in heart rate or a decrease in stroke volume is the primary change in the fetus and newborn. In either case the drive to maintain cardiac output would predict that the two changes would co-exist.

Conclusions

Maternal obesity may be associated with increased heart rate, decreased heart rate variability and decreased ventricular volume in the newborn. These changes may provide a mechanism for the association between maternal obesity and increased cardiovascular risk in offspring. Further studies are clearly required to confirm the associations, examine the impact of confounders and provide an understanding of the responsible metabolic pathways. Awareness of the impact of maternal obesity on newborn heart size and heart rate could inform preconception planning, giving scope for 'primordial prevention'(37) - establishing optimum cardiovascular health to improve outcomes for offspring(38) by preventing risk factors before they have the chance to develop.

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What is already known on this topic

- Maternal obesity is associated with adverse cardiovascular outcomes in offspring
- Fetuses of women with obesity have increased heart rate and decreased heart rate variability

What this study adds

- Infants born to mothers with obesity have increased resting heart rate, decreased heart rate variability, and decreased left ventricular chamber size in the newborn period
- Changes in autonomic function or cardiac growth during pregnancy and early postnatal life may provide a causal mechanism for the association between maternal obesity and increased cardiovascular risk in offspring.
- Modifying antenatal and perinatal maternal health may have the potential to optimize long term cardiovascular health in offspring.

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Table 1 – Demographic Data for Mothers and Infants

Outcome	Maternal BMI 20-25kg/m² (n=56)	Maternal BMI ≧30kg/m² (n=31)	*P* value
Maternal Age at delivery (years), mean (SD)	33.0 (5.2)	31.2 (6.3)	0.19
Maternal BMI first antenatal visit (kg/m²), mean (SD)	22.6 (1.8)	35.6 (4.1)	**<0.001**
Gestation (weeks), at delivery mean (SD)	39.9 (1.1)	40.1 (1.1)	0.41
Birth weight (g), mean (SD)	3499 (466)	3536 (428)	0.71
Infant Body Surface Area (m²), mean (SD)	0.228 (0.022)	0.218 (0.015)	0.14
Main Ethnicity (n)			0.94
White	38	17	
Black	7	5	
Asian	6	1	
Other	5	8	
Socioeconomic Status, household income (n)			**0.015**
<£12,688	7	4	
£12,688-£17,628	1	5	
£17,629-£23,452	1	4	
£23,453-£32,500	2	4	
>£32,500	40	13	
Mode of delivery (n)			0.16
Unassisted Vaginal	19	9	
Operative Vaginal	8	1	
Prelabour LSCS	19	10	
LSCS in labour	10	11	
Maternal Gestational Diabetes	0	1	1.0
Sex of neonate			
Female	24	19	0.15
Male	32	12	

Table 2 – Heart Rate and Heart Rate Variability for Infants Undergoing ECG

Asleep	**Maternal BMI 20-25kg/m^2 (n=45) Mean *(SD)***	**Maternal BMI ≥30kg/m^2 (n=18) Mean *(SD)***	***P* value**
Minimum HR *(bpm)*	91.1 (11.2)	101 (18.6)	**0.01**
Mean HR *(bpm)*	114 (9.8)	123 (12.6)	**0.007**
Maximum HR *(bpm)*	144 (15.4)	148 (11.7)	0.5
SDNN *(ms)*	43.9 (16.5)	34.6 (16.8)	**0.05**
Awake			
Minimum HR *(bpm)*	92.9 (16.4)	101 (24.6)	0.166
Mean HR *(bpm)*	125(15.2)	134 (13.1)	**0.041**
Maximum HR *(bpm)*	157(18.6)	161 (14.4)	0.420
SDNN *(ms)*	48.1 (18.3)	35.6 (14.0)	**0.017**

HR – heart rate; SDNN - standard deviation of normal-to-normal R-R interval

Table 3 – Heart Rate at Time of MRI and Weight-Indexed Biventricular Chamber Volumes and Myocardial Masses in Infants Undergoing MRI Scan

Outcome	Maternal BMI 20-25kg/m² (n=20)	Maternal BMI ≥30kg/m² (n=13)	*P* value
Heart Rate (beats/min), mean (SD)	110 (9.6)	121 (13.9)	**0.01**
Left Ventricular End-Diastolic Volume (ml/kg), mean (SD)	2.54 (0.29)	2.35 (0.14)	**0.03**
Left Ventricular End-Systolic Volume (ml/kg), mean (SD)	0.94 (0.18)	0.85 (0.13)	0.11
Left Ventricular Stroke Volume (ml/kg), mean (SD)	1.60 (0.14)	1.50 (0.09)	**0.03**
Left Ventricular Ejection Fraction (%), mean (SD)	63.2 (3.4)	64.0 (3.9)	0.53
Left Ventricular Output (ml/kg/min), mean (SD)	176 (25)	18 (18)	0.66
Left Ventricular Myocardial Mass (g/kg), mean (SD)	1.72 (0.21)	1.64 (0.23)	0.29
Right Ventricular End-Diastolic Volume (ml/kg), mean (SD)	3.11 (0.30)	2.93 (0.31)	0.12
Right Ventricular End-Systolic Volume (ml/kg), mean (SD)	1.48 (0.18)	1.42 (0.20)	0.41
Right Ventricular Stroke Volume (ml/kg), mean (SD)	1.63 (0.18)	1.52 (0.14)	0.06
Right Ventricular Ejection Fraction (%), mean (SD)	52.5 (3.3)	51.8 (3.5)	0.57
Right Ventricular Output (ml/kg/min), mean (SD)	180 (29)	182 (25)	0.78
Right Ventricular Myocardial Mass (g/kg), mean (SD)	0.82 (0.13)	0.86 (0.13)	0.34

Table 4 – Body Surface Area-Indexed Biventricular Chamber Volumes and Myocardial Masses in Infants Undergoing MRI Scan

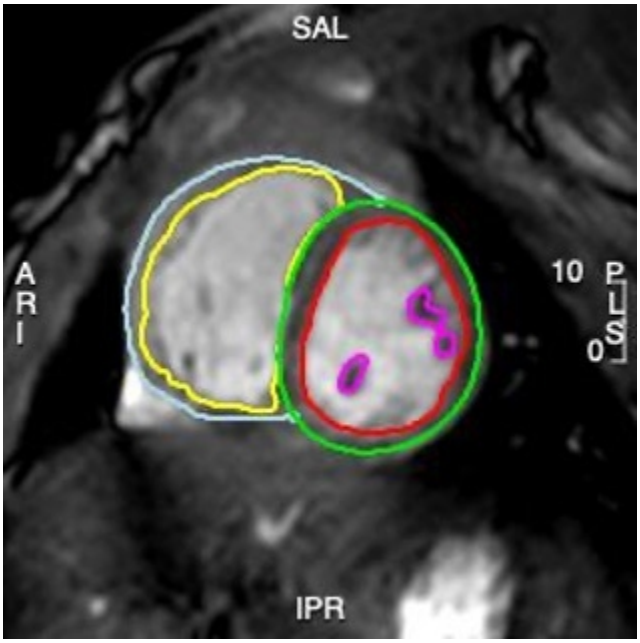
Outcome	Maternal BMI 20-25kg/m^2 (n=16)	Maternal BMI ≥30kg/m^2 (n=12)	*P* value
Left Ventricular End-Diastolic Volume (ml/m^2), mean (SD)	38.8 (4.1)	36.0 (2.3)	**0.045**
Left Ventricular End-Systolic Volume (ml/ m^2), mean (SD)	14.4 (2.5)	13.1 (2.0)	0.17
Left Ventricular Stroke Volume (ml/ m^2), mean (SD)	24.4 (2.3)	22.9 (1.5)	**0.048**
Left Ventricular Myocardial Mass (g/ m^2), mean (SD)	26.3 (2.9)	24.9 (3.7)	0.28
Right Ventricular End-Diastolic Volume (ml/ m^2), mean (SD)	47.2 (4.5)	44.8 (5.1)	0.19
Right Ventricular End-Systolic Volume (ml/ m^2), mean (SD)	22.6 (2.9)	21.7 (3.6)	0.45
Right Ventricular Stroke Volume (ml/ m^2), mean (SD)	24.7 (2.4)	23.2 (2.1)	0.10
Right Ventricular Myocardial Mass (g/ m^2), mean (SD)	12.4 (2.0)	13.0 (2.3)	0.41

Figure legends

Figure 1. Cine steady-state free precession short-axis image demonstrating method of measurement of left and right ventricular mass and volume in end-diastole. Papillary muscles were separately contoured and included in the LV mass calculation

Figure 2. Consort diagram. Women were recruited from the Standard-care arm of the UK Pregnancies Better Eating and Activity Trial (UPBEAT) study, and from either the hospital birth center or the post-natal wards at St Thomas' Hospital, within 72 hours of giving birth. Women were recruited into the obese arm of the study if they had a BMI≥30kg/m^2 whereas women with a BMI 20-25 kg/m^2 were recruited into the normal BMI arm of the study, and were invited to consent for their newborn infants to be included all, or part, of the cardiovascular assessments, including MRI

Figure 3. Mean Heart rate and Heart rate variability (standard deviation of normal-to-normal R-R interval (SDNN)) in neonates born to women with obesity in pregnancy *versus* neonates from normal weight mothers. Values are given as mean and standard deviations



Cine steady-state free precession short-axis image demonstrating method of measurement of left and right ventricular mass and volume in end-diastole. Papillary muscles were separately contoured and included in the LV mass calculation

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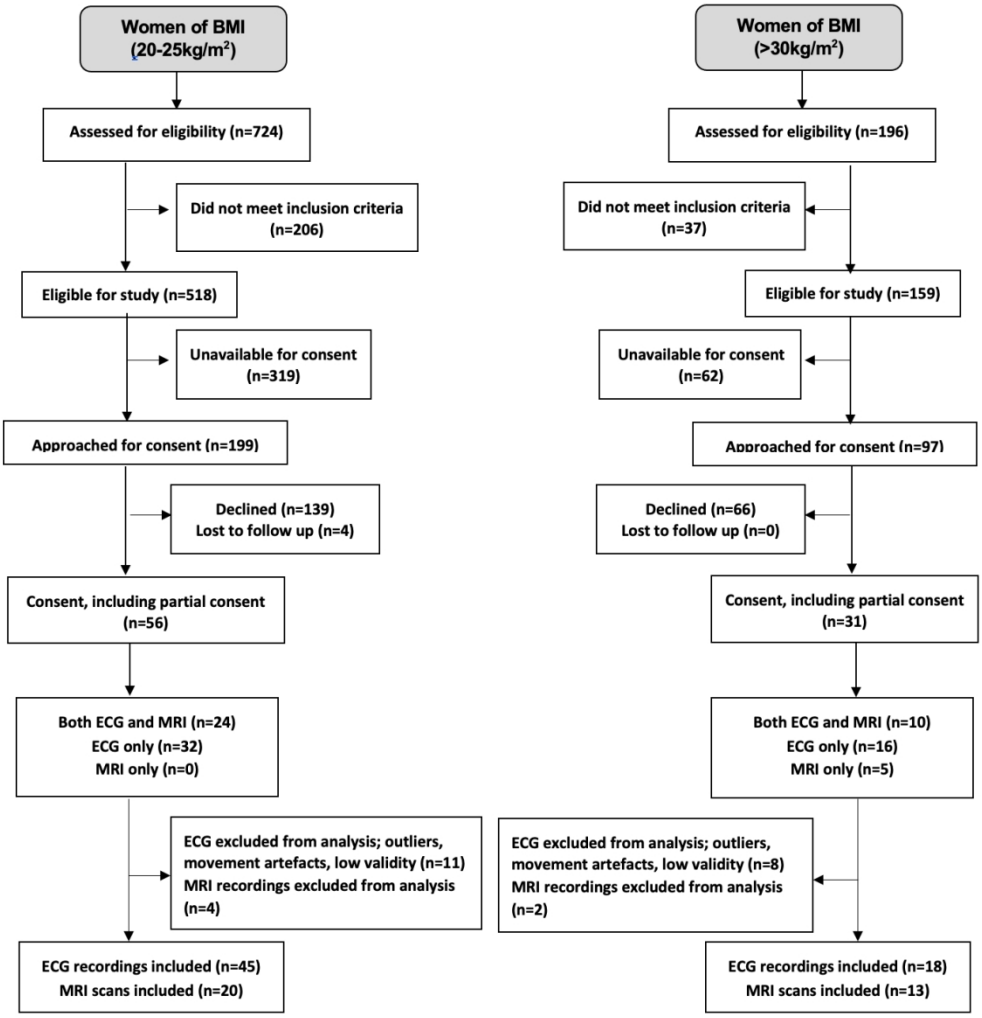

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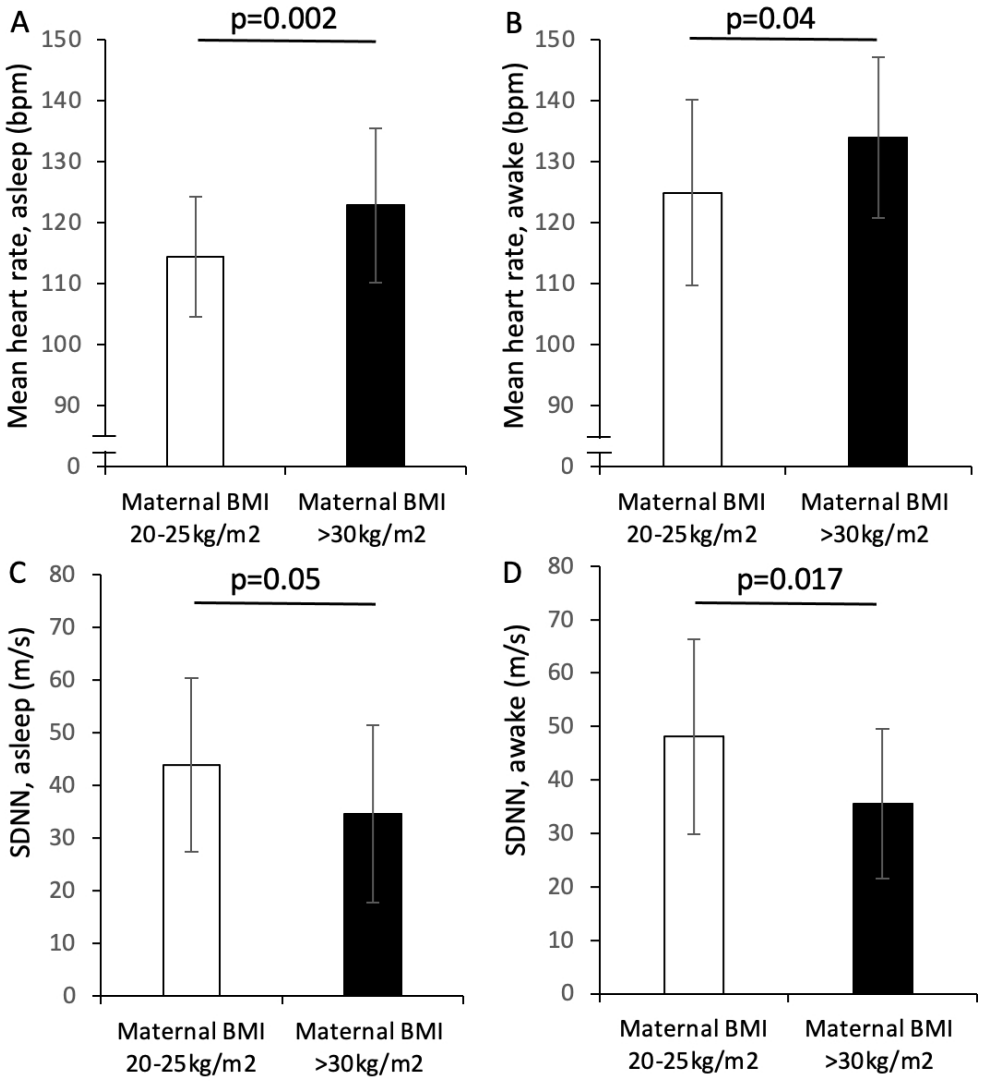

Mean Heart rate and Heart rate variability (standard deviation of normal-to-normal R-R interval (SDNN)) in neonates born to women with obesity in pregnancy versus neonates from normal weight mothers. Values are given as mean and standard deviations

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