The relationship between maternal characteristics and carotid intima-media thickness using an automated ultrasound technique

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Abstract

Carotid intima-medial thickness (CIMT) is a marker of cardiovascular health, though its relationship between maternal characteristics in pregnancy is not widely reported. In this study we aimed to investigate CIMT in healthy pregnant women between 24-40 weeks of gestation and the relationship between CIMT and maternal demographic characteristics using a fully-automated ultrasound technique.

66 normotensive women between 24-40 weeks gestation were prospectively recruited. High-resolution B-mode ultrasound images of the right common carotid artery were obtained from which CIMT was measured using a fully automated technique.

CIMT showed no relationship with gestational age (rho=-0.124, p=0.335). There was no difference between the CIMT measurements between nulliparous and multiparous women (Z=-0.055, *p=0.960*). A relationship was found between CIMT and maternal age (rho=0.277, *p=0.028*), booking BMI (rho=0.278, *p=0.027*) (fig. 5) and BMI at time of recruitment to the study (rho=0.287, *p=0.023*). No correlation was found between CIMT and mean arterial pressure (rho=0.110, *p=0.393*). In our cohort, CIMT ranged from 0.30mm-0.80mm, and the 97.5th percentile of CIMT was 0.63mm. There was no difference in repeated CIMT measurements from the same participant (Z=-0.0348, *p=0.976*).

We report that, in healthy pregnancy, CIMT was related to BMI and maternal age but not parity or gestational age.

Key words: endothelium, imaging, pregnancy, ultrasound

Introduction

Carotid intima-media thickness (CIMT) is commonly used to assess subclinical atherosclerosis and cardiovascular risk. CIMT has been found to be increased in pre-eclamptic pregnant women compared to normotensive pregnant women and therefore may have a role in antenatal care to identify women at high risk of pre-eclampsia (1). However, more studies are required to establish the normal range of CIMT in pregnancy before such test can be implemented in the clinical setting.

Pre-eclampsia is defined as new onset hypertension and significant proteinuria (Urine protein creatinine ratio >30) post 20 weeks gestational age (GA) (2)(3). It is well known that endothelial dysfunction is an important factor in the development of pre-eclampsia. Recent studies have suggested that pre-eclamptic women have greater evidence of atherosclerosis than normotensive pregnant women (4)(5). Thus, there is interest in the potential use of markers of subclinical atherosclerosis during pregnancy to predict women at risk of developing pre-eclampsia.

A commonly used marker of subclinical atherosclerosis is CIMT. Arterial walls consist of three layers: the intima, the media and the adventitia. CIMT encompasses the collective thickness of the intima and media layers of the carotid artery (Fig. 1). As a consequence of atherosclerosis CIMT is greater, which is a known indicator of cardiovascular risk (6).

Ultrasound techniques can be used to visualise the carotid artery in real-time and obtain images from which CIMT can be determined. The carotid artery is particularly easy to locate due to its relatively large size, pulsatility and superficial anatomical location and thus can usually be imaged with minimal difficulty. Software packages can be installed onto ultrasound imaging devices used in clinical settings to allow for automated calculation of CIMT (7). Automated software offer the benefit of reducing the requirement of specific operator training and provide a more standardised method of intima-media identification and measurement (6).Such packages may be considered for use in risk stratification in the antenatal period.

A previous study suggested that CIMT could be used to predict pre-eclampsia in the

first trimester with 76.9% sensitivity (1). Assessment of CIMT postpartum may be beneficial in recognising women of high cardiovascular risk following pre-eclamptic pregnancies and providing lifestyle interventions and appropriate surveillance (4).

Few published studies explore CIMT in normotensive low-risk pregnancies. No significant difference between CIMT in healthy pregnant and non-pregnant women has been found (8). CIMT values measured in 38 pregnant women found no correlation between CIMT and GA (9). However, more research is needed to establish the relationship between CIMT and GA and to identify a normal reference range for CIMT in pregnancy before clinical use in prediction and management of pre-eclampsia. Therefore, this study aimed to determine the upper limit of CIMT in normal healthy pregnant women between 24-40 weeks of gestation and the relationship of CIMT with baseline maternal demographic characteristics.

Methods

Participants

66 healthy women between 24 and 40 weeks GA were recruited prospectively in a tertiary care maternity unit. Exclusion criteria for this study included: multiple pregnancy, a known underlying maternal cardiovascular condition, maternal hypertension defined as ≥140mmHg systolic blood pressure (BP) and/or ≥90mmHg diastolic BP at time of visit, fetal abnormality, body mass index (BMI) ≥40 or self-reported smoking during pregnancy. Written and informed consent was acquired from all participants.

Data collection

BMI and BP measurements recorded at time of first antenatal booking appointment were obtained from the participant's hand held medical records. Weight was recorded at the time of recruitment to the study. A single BP reading at time of recruitment was measured using the Vicorder™ (Skidmore Medical, Bristol, UK). The BP measurement was recorded from the right arm with the participant in the left lateral lying position (10). All measurements were obtained in a quiet and cool room between 8am and 5pm. Before obtaining measurements, participants were rested for at least 10 minutes.

Ultrasound technique

All measurements were obtained using the Samsung™ HS70A ultrasound system (Samsung™ Medison, Seoul, South Korea). The ultrasound system was used in accordance with training provided by the manufacturer.

Participants were in a semi-recumbent position with their head rotated to the left. High-resolution B-mode ultrasound cine-loops of the right common carotid artery (RCCA) in a longitudinal section were obtained using a L3-12A probe. Multiple cine-loops were saved for each participant and the 2 cine-loops that depicted the RCCA in the clearest, most horizontal position, as deemed by the operator, were selected for analysis.

CIMT values were obtained using a fully-automated technique. A cine-loop was automatically analysed and the automated technique measured CIMT at a predefined point at which the measurement was more reproducible. The intima-media boundary of a segment of the far wall of the RCCA was determined by the automated software. The minimum and mean CIMT values were calculated from the segment selected and the mean CIMT was recorded (Fig. 2). If the intima-media layer of the distal wall of the RCCA was incorrectly identified, the selected boundaries of the intima-media layer were edited and corrected. A manual measurement of CIMT was also obtained from the same ultrasound images by the same operator.

Statistical analysis

Data analysis was carried out using Microsoft Excel and SPSS Version 23 (IBM Corporation, Armonk, New York, USA). Histogram plots were used to assess the data for normal distribution. Normally distributed data were displayed as means and standard deviations (SDs), while non-normally distributed data were displayed as medians and interquartile ranges (IQRs). Mean arterial pressure (MAP) was calculated as $\frac{systolic\ blood\ pressure+(2\times diastolic\ blood\ pressure)}{3}$ using the BP measurement taken at time of recruitment and CIMT measurement.

Spearman's bivariate correlation was used to determine the relationship between fully-automated CIMT measurements and baseline maternal demographic characteristics including maternal age, GA, BMI, booking BMI and MAP. A Mann-Whitney U test was performed to assess the difference between fully-automated CIMT measurements of nulliparous and multiparous women. A Wilcoxon signed rank test was performed using repeated fully-automated CIMT measurements from the same participant to assess reproducibility. A *p value <0.05* was regarded as statistically significant. A Bland-Altman plot was constructed to assess the level of agreement between the fully automated technique of CIMT measurement and manual measurement of CIMT from ultrasound images.

Ethical approval for this study, which was part of a larger study on cardiovascular function in pregnancy, was received from NRES-Committee, London Riverside

Research Ethics Committee (REFERENCE 15/lo/0341). NHS R&D approval was granted by the Imperial College Joint Research Compliance Office (15HH2516).

Results

66 pregnant women were offered recruitment of whom three were excluded due to multiple pregnancy, new onset pathology or current smoking status. Demographics and overall results of the 63 participants included are displayed in Table 1.

There was no relationship between GA and CIMT (rho=-0.124, *p=0.335*) (Fig. 3). The mean CIMT measurement at each GA epoch is shown in Table 2. Of the 63 participants included in the study, 31 women were multiparous and 32 were nulliparous. There was no significant difference between the CIMT measurements from nulliparous and multiparous women (Z=-0.055, *p=0.960*).

CIMT measurements ranged from 0.30mm to 0.80mm. The upper limit (97.5^{th} percentile) of CIMT between 24-40 weeks of gestation was 0.63mm.

No correlation was found between CIMT and Mean arterial pressure (MAP) (rho=0.110, *p=0.393*). However, there was a relationship between CIMT and maternal age (rho=0.277, *p=0.028*) (Fig. 4), BMI at time of recruitment to the study (rho=0.287, *p=0.023*) (Fig. 5) and BMI at time of antenatal booking appointment (rho=0.278, *p=0.027*) (Fig. 6). There was no significant correlation between CIMT and the difference between booking BMI and BMI at time of recruitment (rho= -0.123, *p= 0.337*) (Fig 7).

There was no difference between the two CIMT measurements obtained from two different ultrasound images from the same participant (Z=-0.0348, *p=0.976*).

A Bland-Altman plot was constructed to assess the level of agreement between the fully automated technique of CIMT measurement and manual measurement of CIMT from ultrasound images. The bias was 0.065mm and the upper and lower limits of agreement were 0.245 and -0.114 respectively (Fig 8).

Discussion

This prospective cohort study, using a fully automated ultrasound measurement technique, found CIMT did not vary with GA in the late second and third trimesters in accordance with previous studies. To our knowledge, no other study has been conducted with the aim of determining the upper limit of CIMT in normotensive pregnancy; this knowledge is important particularly in the context of pathological pregnancy. We report that CIMT is associated with both BMI, consistent with a previous study (9), and maternal age. Studies in men and non-pregnant women showed CIMT significantly correlated with age (11)(12). As CIMT is a known marker for atherosclerosis (13), these findings are unsurprising, as it has previously been recognised that age and BMI are risk factors for atherosclerosis(14)(12). Besides increased atherosclerosis, this may be a result of an increase in carotid systolic BP seen in older individuals, which is thought to encourage hypertrophy of the arterial wall and therefore an increase in CIMT (15).

No difference in CIMT was found in nulliparous and multiparous pregnant women (t=0.5043, *p=0.6163*). A previous study found a significant correlation between parity and CIMT, however this correlation was lost when CIMT was adjusted for age (16). As the mean age of the multiparous and nulliparous women were very similar in our study, this could support the contention that the correlation found in the previous study was a consequence of age and not parity.

The upper limits of CIMT in healthy men and non-pregnant women have been reported as 0.60mm for 35-39 years of age and 0.64mm for 40-49 years of age (17); similar to the upper limits of CIMT found in our cohort. In accordance with previous studies, this may suggest that CIMT does not increase from pre-pregnancy to pregnancy (8). Additionally, CIMT was not associated with advancing GA between 24 to 40 weeks gestation suggesting reference ranges specific to GA epochs during this period of gestation are not necessary.

A previous study measured CIMT in 600 pregnant women and concluded CIMT was significantly increased in pre-eclampsia compared to normotensive pregnancies from

the first trimester, (1) with other studies reaffirming these findings (18)(19)(4). To our knowledge, very limited studies have been conducted exploring CIMT during normal pregnancy. These studies are important in determining normal CIMT parameters during pregnancy, if CIMT is to be available in clinical practice as a tool for pre-eclampsia diagnosis and/or management.

CIMT reproducibility has been identified as superior in automated techniques as opposed to manual measurement (17). Previous studies suggest that CIMT was greater at the bifurcation than at the common carotid artery (17), highlighting the importance of standardisation in the section of the carotid artery assessed by ultrasound technique. Furthermore, ultrasound images of the arterial wall are two-dimensional, whereas atherosclerosis is three-dimensional and presents very irregularly. Therefore, the CIMT value obtained is influenced by the angle at which the artery is imaged and the segment of the vessel wall analysed (20). An advantage of the ultrasound technique is that it allows direct visualisation of the artery, permitting the operator to ensure the same anatomical site is assessed. However adequate operator training is necessary to ensure standardisation in technique, if CIMT measurements were to be routinely introduced into medical practice.

A recent study suggested that intima/media ratio (I/M) is a more sensitive measure of atherosclerosis than CIMT (18). During atherosclerosis, the thickness of the intimal layer increases whilst the medial layer decreases, causing the intima/media ratio (I/M) to increase more so than the increase in CIMT, suggesting that I/M is a better predictor of pre-eclampsia than CIMT (18). To our knowledge, this is the only study exploring I/M versus CIMT in prediction of pre-eclampsia. It is difficult to draw conclusions based on a single study with limited numbers, therefore more comparison studies are necessary to establish which is the superior measure.

We were able to prospectively recruit across all GA epochs required for the study, permitting a good representation of mid-late pregnancy. Furthermore, a fully-automated technique was used to obtain CIMT measurements, which allowed for a standardised technique and reduced operator bias. Liaison with the manufacturer's representative, ensured the technique was used as per

recommended instructions. A limitation of this study is that although one half or the women studied were non-caucasian, the numbers were too small to preclude meaningful analysis of the relationship between CIMT and maternal ethnicity.

Conclusion

CIMT has a positive association with maternal age and BMI in healthy pregnant women. For 24-40 weeks gestation, no correlation was found between CIMT and GA and the upper limits of CIMT was 0.63mm.

It is clear further studies are required to establish a reference range for CIMT during normal healthy pregnancy before application on pathological pregnancies. Future research should also explore the requirement for age and ethnicity specific reference ranges for CIMT in pregnancy. The ease of the fully-automated ultrasound technique suggests that it may be applicable as a non-invasive bedside test for CIMT in pregnant women.

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Declaration of interest statement

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Tables

Demographics	**Mean (SD)**
Age (y)	34.02 (5.40)
BMI (kg/m^2)	27.65 (3.66)
Booking BMI (kg/m^2)	24.07 (3.65)
MAP (mmHg)	74.97 (7.17)
GA (weeks)	29 (6)*
Ethnicity	**N**
Caucasian	32
Asian	19
Mixed	3
Other	9
Parity	**N**
Nulliparous	32
Multiparous	31

Table 1: Participant demographics. Means and Standard deviations (SD) are included where stated. Values with asterisks (*) are median values with interquartile range in parantheses to represent non-normally distributed data.

Abbreviations: Body Mass Index at time of study participation (BMI), Mean Arterial Pressure (MAP), Gestational age (GA), Carotid initma-media thickness (CIMT).

Gestational age (weeks)	N	Mean CIMT (SD) (mm)
24^{+0}-27^{+6}	11	0.40 (0.05)
28^{+0}-31^{+6}	31	0.44 (0.10)
32^{+0}-35^{+6}	13	0.42 (0.08)
36^{+0}-40	8	0.39 (0.09)
Overall: 24-40	63	0.42 (0.09)

Table 2: Arterial assessment parameters in normotensive pregnancy between 24 to 40 weeks of gestation. The mean measurements of participants at each gestational age epoch is shown. Standard deviations are stated in parentheses.

Figures

Figure 1.

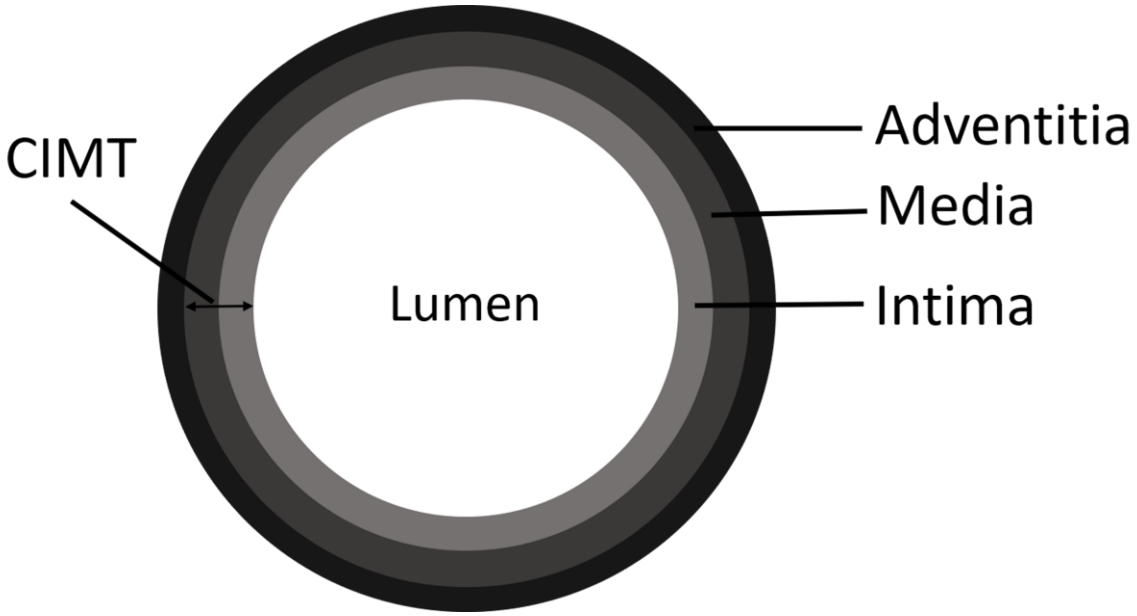


Figure 2.

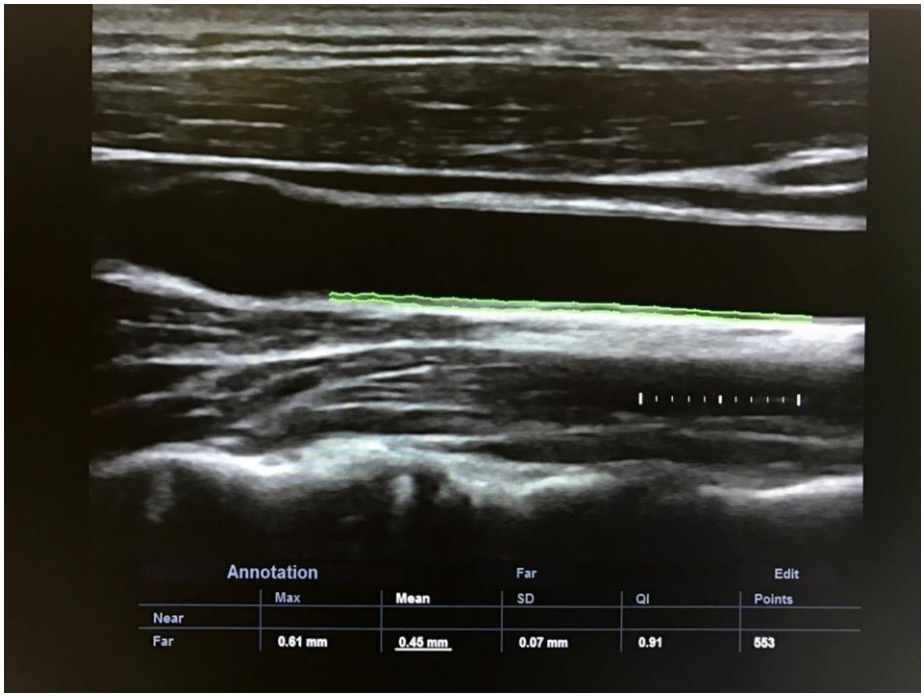
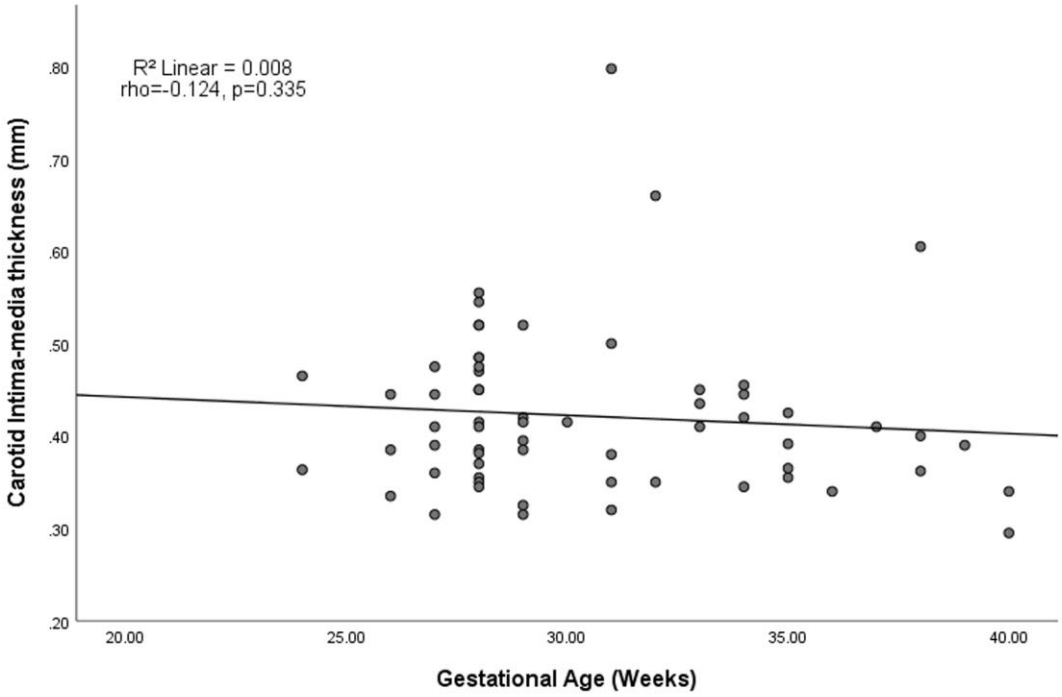


Figure 3.



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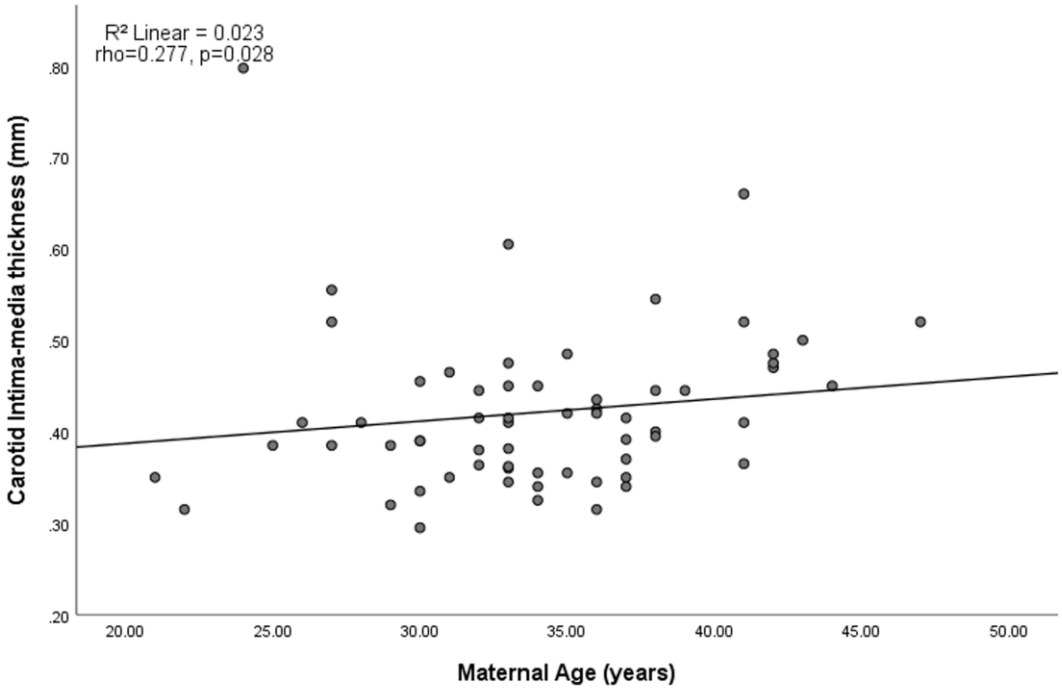

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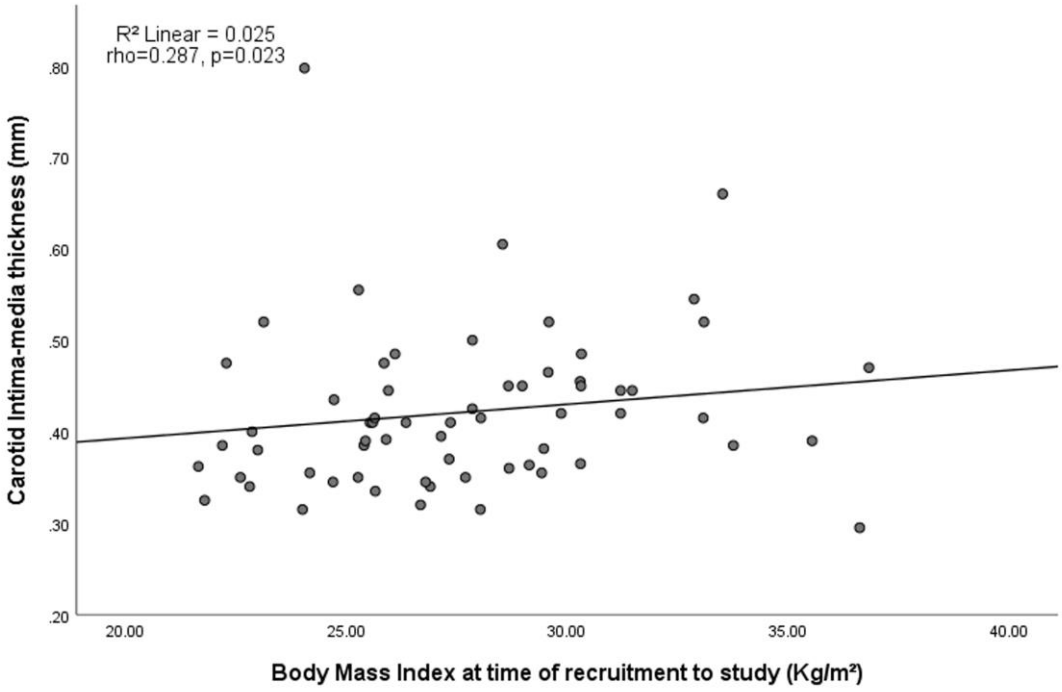

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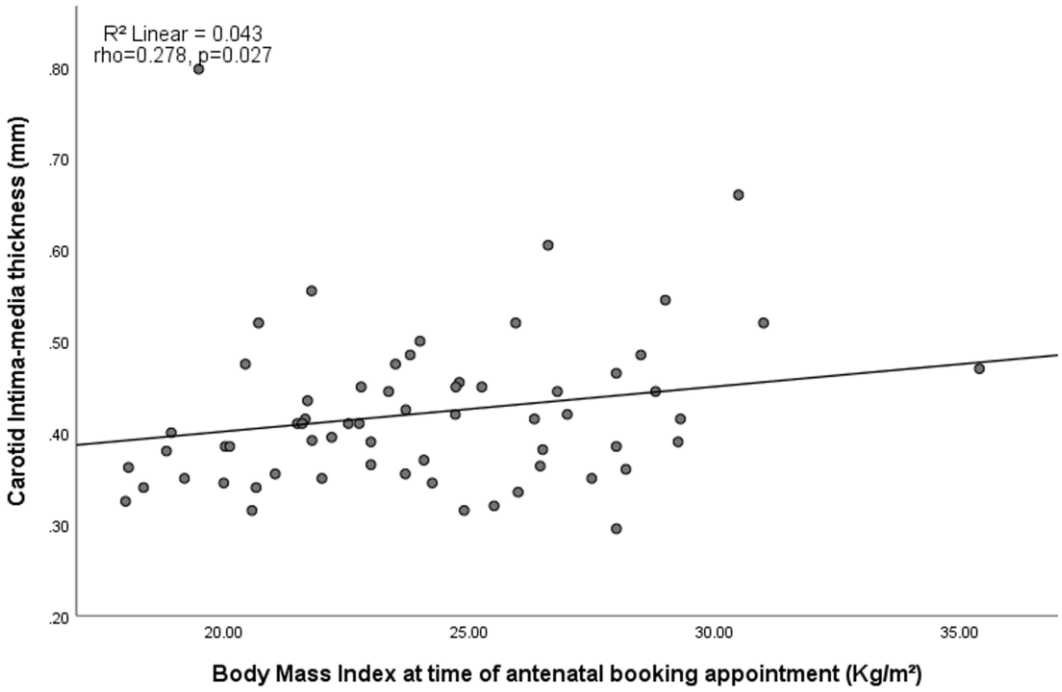

Figure 7.

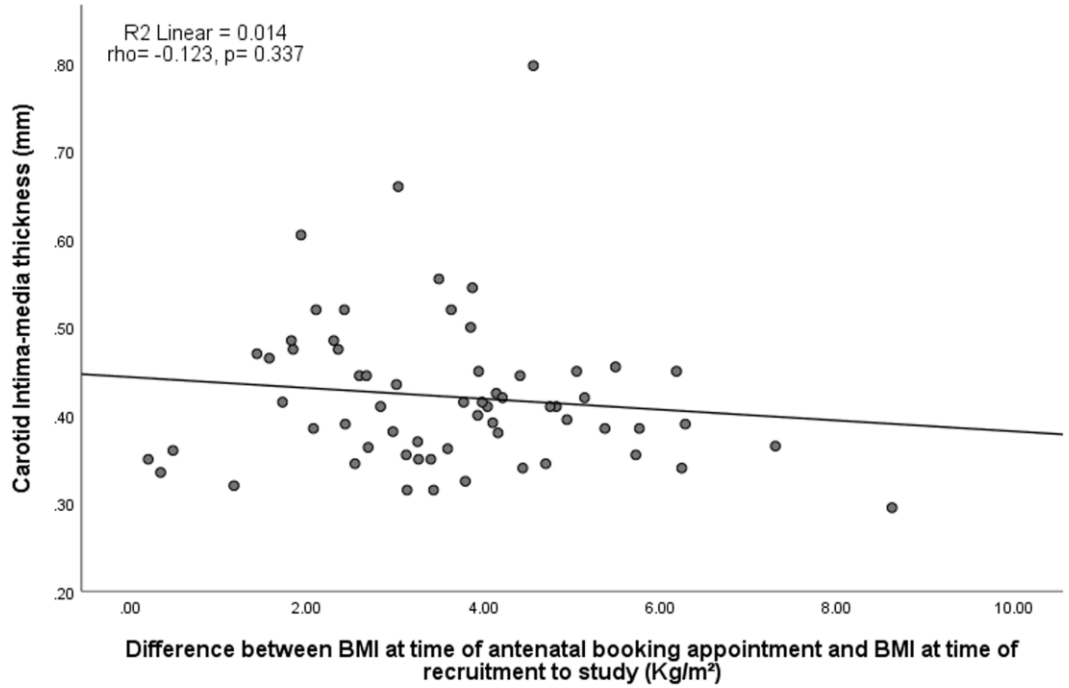

Figure 8.

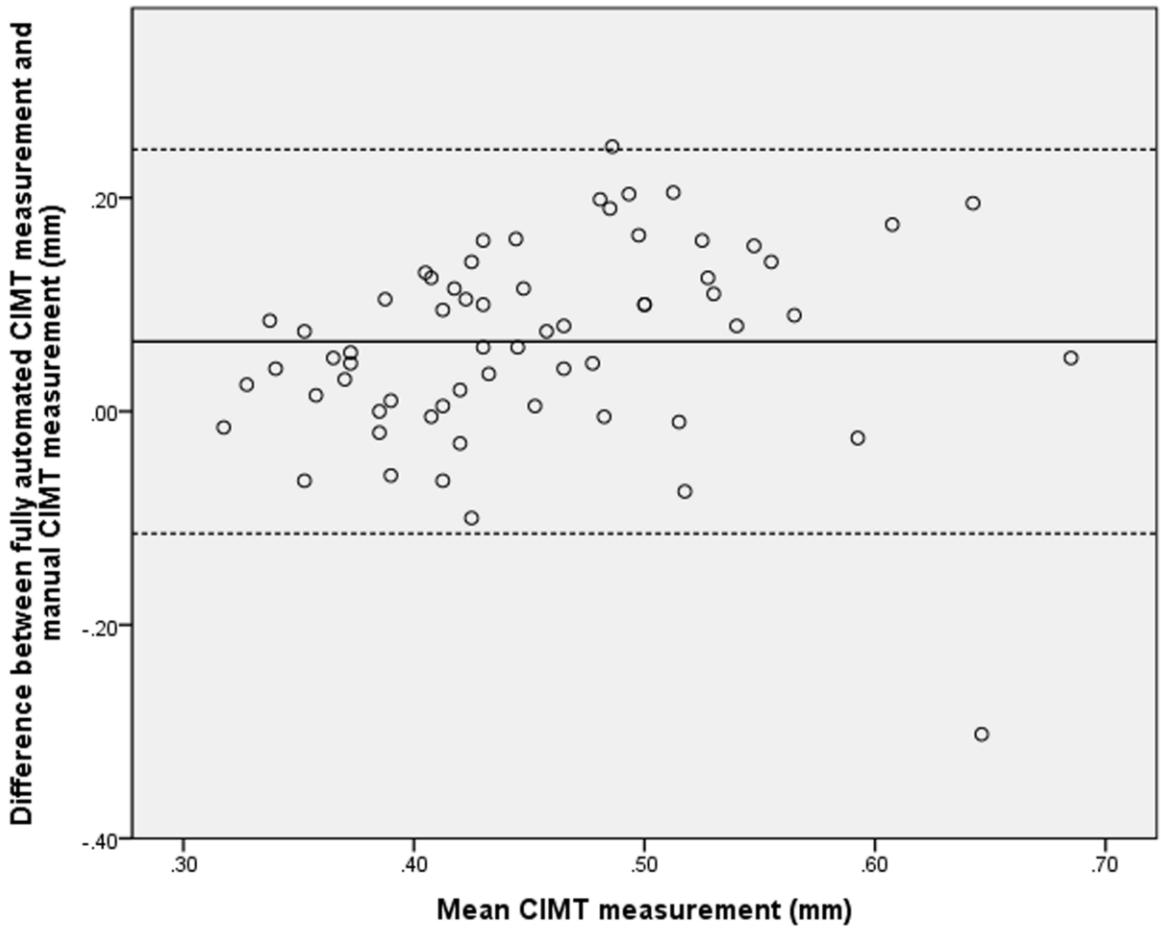

Figure captions

Figure 1: Cross-sectional view of the carotid artery. The arterial wall is made of three layers: the intima, media and adventitia. The carotid intima-media thickness (CIMT) is the combined thickness of the intima and media layers of the arterial wall.

Figure 2: Automated intima-media thickness measurement using ultrasound images. The intima-media boundary of the near wall of the right common carotid artery was automatically contoured. The maximum and minimum intima-media thickness were determined from the segment analysed and the mean carotid intima-media thickness value was calculated.

Figure 3: Scatter graph showing the correlation between gestational age and carotid intima media thickness

Figure 4**:** Scatter graph showing the correlation between maternal age and carotid intima media thickness

Figure 5: Scatter graph showing the correlation between maternal body mass index at time of recruitment and carotid intima media thickness

Figure 6: Scatter graph showing the correlation between body mass index at time of antenatal booking appointment and carotid intima media thickness

Figure 7: Scatter graph showing the correlation between the difference in body mass index at time of antenatal booking appointment and recruitment to study and carotid intima media thickness

Figure 8: Bland-Altman plot to show the level of agreement between the fully automated technique of CIMT measurement and manual measurement of CIMT from ultrasound images. The bias was 0.065 and the upper and lower limits of agreement were 0.245 and -0.114 respectively.