Influence of maternal characteristics and gestational age on haemodynamic indices: NICOM device-specific reference ranges

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Running Head: A reference range of haemodynamics measured by NICOM® in pregnancy

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ABSTRACT

Background: There is increasing evidence for the importance of haemodynamic monitoring in pregnancy. Device-specific reference ranges are required in order to correctly intepret hemodynamic indices in healthy and pathological pregnancies.

Methods: This was a prospective cohort study of healthy singleton pregnancies. Haemodynamic measurements of stroke volume, cardiac output and systemic vascular resistance throughout pregnancy were obtained using NICOM®, a non-invasive device based on bio-reactance technology. NICOM device-specific reference ranges were created with respect to gestational age and maternal characteristics.

Results: We included 411 women in this study. The relationships shown between cardiac variables and gestational age shown in the NICOM-specific reference ranges are consistent with previous findings, with an increase in cardiac output until around 35 weeks before a decrease to term and converse changes in systemic vascular resitance. Maternal weight, height and age were associated with cardiac output (all $p<0.05$) and systemic vascular resistance (all $p<0.01$), whilst maternal weight and height were associated with stroke volume (both $p<0.001$). Ethnicity was significantly associated with stroke volume ($p<0.05$) but not with cardiac output or systemic vascular resistance.

Conclusions: This study presents device-specific reference ranges for stroke volume, cardiac output and systemic vascular resistance for the NICOM® device in pregnancy and describes the maternal characteristics that are associated with the values of these haemodynamic measurements. Studies using NICOM® in pregnancy can use these ranges in order to evaluate observations relative to those expected in uncomplicated pregnancies conditional on maternal characteristics.

INTRODUCTION

There is increasing evidence that the maternal cardiovascular system has a role to play in pregnancy complications including preeclampsia (PE) and fetal growth restriction (FGR).[1,2] Whilst echocardiography studies have demonstrated clear structural and functional changes in pathological pregnancies, this modality is not feasible on a large scale due to the technical competence required to perform it. Several non-invasive devices are now available to measure parameters of central haemodynamic function, namely stroke volume (SV), cardiac output (CO) and systemic vascular resistance (SVR). Using these devices, researchers have demonstrated differences in the cardiovascular function of women with healthy and pathological pregnancies.[3–5] However, with multiple different devices being used, it is imperative that device-specific reference ranges are created, and used when intepreting and reporting the results. We have previously demonstrated the differences in the obtained haemodynamic indices in normotensive and hypertensive pregnancies using two different devices (USCOM-1A® and NICOM®), highlighting that they cannot be used interchangeably.[6] Similarly, we have previously compared these two non-invasive devices to transthoracic echocardiography, showing good agreement only in the third trimester for each device.[7] We have also compared NICOM® to a minimally-invasive device (LiDCO*rapid*) in a pregnant population and shown that they should not be used interchangably.[8] It is clear that the output from these new devices should not be interpreted using existing echocardiography reference ranges, and that device-specific ranges are required. Therefore, we have previously published device-specific reference ranges for USCOM.[9]

The aim of this study was to create reference ranges for SV, CO and SVR in pregnancy for the NICOM® device and to explore associations between maternal characteristics and these haemodynamic variables.

METHODS

Study Design and Population

This was a prospective cohort study in low-risk pregnant women attending a tertiary referral hospital between September 2012 and May 2018. Inclusion criteria were women with an uncomplicated singleton pregnancy between 10 and 40 weeks' gestation attending antenatal care at St George's Hospital, London, UK. Exclusion criteria included any medical disorder present at the time of study recruitment, or development of hypertension or FGR following study recruitment. Pregnancies complicated by major fetal anomalies, aneuploidy or intrauterine fetal demise were excluded. Gestational age was calculated from the crown–rump length measured at 11–13 weeks' gestation or head circumference if the first ultrasound scan was performed after 14 weeks gestation.[10] Demographic and pregnancy details including age, height and weight at booking and study recruitment, ethnicity, use of assisted reproductive techniques (ART), smoking status, parity and medical history were obtained and recorded. Patients were followed up and pregnancy outcomes were obtained from maternity databases. Gestational hypertensive disorders were defined as per the ISSHP criteria and FGR was defined as per the Delphi consensus definition.[11,12] Written consent was obtained from all study participants and local research ethics committee approval (12/LO/0810) was obtained prior to data collection.

Haemodynamic Assessment

NICOM® (Cheetah Medical, Boston, MA, USA) is a completely non-invasive device which uses thoracic bioreactance technology to estimate hemodynamic indices. At recruitment, maternal height and weight were measured. The NICOM® electrodes were placed on the posterior thorax of the patient as per the manufacturer's instructions. Participants sat quietly for 10 minutes prior to starting the haemodynamic assessment. The participants' details, including current height and weight were entered into the machine and the device was calibrated whilst the patient was lying still in a semi-recumbent position. Participants were requested not to talk or move during the study. Measurements were recorded every 30 seconds. We used the fifth measurement to allow a further two minutes of rest and allow patients to get used to the recording. Blood pressure was recorded using the integrated,

automated NICOM® cuff. The arm circumference was measured to ensure the correct size cuff was used. The three variables of interest in this study were SV, CO and SVR.

Statistical analysis

Models were fitted using the *gamlss* package for R (R Foundation, Vienna, Austria).[13] Improvements in model fit were evaluated using the generalised likelihood ratio test, with statistical significance at $P<0.05$. For each cardiac variable, a normal distribution with mean conditional on gestational age was considered first. The relationship of the mean with gestational age was flexibly modelled using a natural cubic spline (NCS) basis, with boundary knots at the 5th and 95th centiles (79.5 and 269 days, respectively) and internal knots at the 10th, 25th, 50th, 75th and 90th centiles (85, 93, 153, 251 and 263 days, respectively), if this provided a better model fit than a linear association. The standard deviation was then also allowed to vary with gestational age, using either a linear function or a NCS basis if used for the mean with the same boundary knots but with an internal knot at only the 50th centile. The model was then extended in each case to allow for a skewed distribution using the Box–Cox, Cole and Green (BCCG) distribution, and then to also adjust for the kurtosis (or 'tailedness') of the data using the Box–Cox power exponential distribution (BCPE).[14] For the BCCG and BCPE distributions, the median and scale parameter were modelled as smooth functions of gestational using NCS, and the skewness and kurtosis parameters were estimated as constants. Plots of standardized residuals were checked.

Once the distribution of the data had been determined with respect to the gestational age, patient characteristics that might plausibly be associated with the cardiac variables were added to the model to test whether they provided a significant improvement in prediction of the mean/median value. Maternal examination weight and height were added to the models first, each using a cubic spline basis with boundary knots at the 10th and 90th centiles and internal knots at the 50th centiles (57.0, 70.6 and 95.8 kg, and 1.56, 1.64 and 1.74 m, respectively), and an interaction term (centred at the medians) was then added for weight and height. A constant effect of (any) smoking during pregnancy was then tested, followed by the addition of maternal age using a NCS basis with boundary knots at the 10th and 90th centiles and an internal knot at the 50th centile (25, 32 and 38 years, respectively). Finally, the effects of having conceived using ART, being nulliparous and ethnicity (groupings: Afrocarribean, Caucasian, South Asian, Other Asian, Mixed/other) were tested.

RESULTS

We recruited 455 patients to this study. No patients withdrew their consent, but 11 patients were excluded from the analysis due to the development of fetal or maternal complications and in 33 patients observations were obtained outside of the GA range considered, leaving measurements from 411 women to form the reference ranges. One woman was missing a measurement for SV and two were missing a measurement for SVR. The number of measurements for each gestational week ranged from one to seventy-one (Figure 1). Baseline demographic data is shown in Table 1. The NICOM-specific reference ranges, displaying the 5th, 50th and 95th centiles for SV, CO and SVR, are shown in Figure 1 and centile calculators for CO, SV and SVR are provided in supplementary material 1. The normal distribution was adequate to model SV and CO, but the BCPE distribution provided an improvement in model fit for SVR. Increasing median values of CO were observed from 10 weeks until around 35 weeks, with a subsequent decrease until term. SV showed a small linear increase across gestation with lower variability in observations close to term, the use of NCS did not provide an improvement in model fit in this case (P=0.070). There was a reduction in the median value of SVR from 10 weeks until around 32 weeks, followed by an increase towards term.

Associations with maternal characteristics

Maternal weight (P<0.001), height (P=0.028) and age (P<0.001) were associated with CO. There was no significant interaction between weight and height (P=0.138). Both larger values of maternal height and weight were independently associated with higher CO (Figure 2a). The estimated median cardiac output showed a linear decrease with maternal age, being around 0.5 L/min lower for a woman aged 35 compared to a woman aged 25 years (Figure 3a). No further significant improvements in model fit were gained by the addition of ethnicity (P=0.073 for overall model comparison), smoking (P= 0.304), ART status (P=0.209) or nulliparity (P=0.135).

Maternal weight (P<0.001) and height (P<0.001) were associated with SV, but there was not significant interaction between these variables (P=0.105). Stroke volume was higher for taller women and there was also a positive independent association with maternal weight (Figure 2b). No further improvement to model fit was provided by smoking (P=0.700), maternal age (P=0.216), ART status (P=0.944) or nulliparity (P=0.753). Ethnicity was significantly associated with SV (P=0.001, for overall model comparison), with women of South Asian (estimated mean difference -12.2 mL, 95%CI -18.7 to -5.8) and other Asian ethnicities (-8.4 mL, -15.3 to -1.6) having lower values relative to Caucasian women but no significant difference observed for women of Afro-Caribbean ethnicity (-2.5 mL, -7.4 to 2.5).

Maternal height (P<0.001) and weight (P=0.002) were independently associated with SVR, but there was not a significant interaction between these variables (P=0.772). Increasing height and weight were both associated with lower SVR values (Figure 2c). Greater maternal age was associated with higher SVR values (P=0.004) (Figure 3b), and nulliparity was also associated with higher SVR (estimated mean difference 45.2 dynes/sec/cm^2, 95% CI 2.5 to 87.9, P=0.038). No further improvement to model fit was provided by smoking (P=0.967), ART status (P=0. 575) or ethnicity (P=0.128).

DISCUSSION

Summary of study findings

Our study reports reference ranges of SV, CO and SVR in pregnancy for the NICOM® device. Statistical modelling demonstrated a significant effect of maternal weight, height and age on CO, of weight, height and ethnicity on SV and of weight, height, maternal age and parity on SVR.

Interpretation of study findings and comparison with the existing literature

This is one of the largest study of maternal haemodynamics in healthy pregnancies using the NICOM® device to be published, and the first to offer reference ranges displayed as a centile for SV, CO and SVR at any gestation. The finding of an increase in CO until the mid-third trimester before a fall until term and converse findings with SVR are in keeping with existing studies and knowledge of cardiovascular function in normal pregnancy.[15,16]

Others have used the NICOM® device to study healthy pregnant women. Stott *et al.* used NICOM® in a cohort of 300 healthy pregnancies to create a reference range for subsequent comparison with a cohort of hypertensive women.[4] However, their reference range is not available for use by others and the authors displayed their results as Z-scores rather than centiles. They too found that increased body surface area (BSA) was associated with greater CO, however found no association between maternal age and haemodynamics. They reported increased CO in Afrocarribean women compared to Caucasian women, which we did not find. Monteith *et al.* performed serial measurements in 318 healthy primiparous women from 14 to 28 weeks gestation and compared the results with women from the same cohort who developed hypertension or FGR.[17] They reported similar findings in terms of the longitudinal changes of CO and SVR, but their study is limited by the lack of measurements in the late third trimester. Our group has previously reported reference ranges for the USCOM® non-invasive device, which demonstrated similar longitudinal changes in hemodynamic indices in pregnancy.[9]

Study limitations and strengths

The main strengths of our study are that it includes a large cohort of healthy women across gestation, allowing reference ranges to be constructed between 10 and 40 weeks of

pregnancy. Furthermore, the women were from a range of ethnic backgrounds. The strengths of the statistical modelling technique used are that it is flexible and has considered maternal characteristics that may affect haemodynamic measurements when creating the ranges. One limitation of our study is that we did not perform serial measurements in the same women which would have demonstrated the 'true' longitudinal changes in haemodynamics. However, this is counteracted by having a large cohort with a good distribution of measurements throughout different gestations. Similarly, we did not record any pre-conception or post-natal measurements and are therefore unable to determine the difference in pregnancy measurements compared to baseline with the NICOM® device. It should be kept in mind that NICOM® only previously demonstrated good agreement with echocardiography in the third trimester of pregnancy[7] and has not been compared to an invasive CO monitor in pregnancy.

Clinical and research implications

Studies have demonstrated important changes in maternal haemodynamics using NICOM® and other non-invasive devices in PE and FGR and these measurements have been tested as a screening and prognostic tool as well as to compare the effects of antihypertensive medication.[4,5,18–21] It is therefore likely, that in time, their use will become more widespread and potentially routine in clinical practice. Having a device-specific reference range will allow researchers to further explore the aforementioned findings and strengthen the quality of their research by comparing to a consistent normal range, rather than using different cohorts of control pregnancies with each study. A device-specific reference range will also allow easier transition into clinical practice.

There is increasing evidence and awareness of the association between hypertensive disorders of pregnancy and cardiovascular disease and hypertension up to 20 years postpartum.[22] Furthermore, the risk of subsequent hypertension and cardiovascular disease is related to the severity and gestational age of onset of disease, with a greater risk of hypertension and cardiovascular death in women with early-onset (<34 weeks) PE or with FGR compared to later-onset PE or gestational hypertension.[23,24] The structural and functional cardiac changes observed in PE have also been demonstrated to persist up to 2 years postpartum.[25] Comparing a woman's haemodynamic profile taken with NICOM® in

pregnancy to a reference range, may have a role in screening her for later life cardiovascular risk.

Conclusion

We have presented device-specific reference ranges for SV, CO and SVR for the NICOM® device in pregnancy and described the maternal characteristics that influence these haemodynamic parameters. Future studies using NICOM® in pregnancy can use these ranges to help describe their results.

Conflict of Interests

The authors report no conflicts of interest.

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Figure legends:

Figure 1. Scatter plots of maternal cardiac measurements against gestational age, with median (red line) and 5th and 95th centiles (blue dashed lines) from fitted models also shown. The plots relate to (a) cardiac output and (b) stroke volume and (c) systemic vascular resistance.

Figure 2. Contour plots of (a) cardiac output (b) stroke volume and (c) systemic vascular resistance in a 25-year-old parous Caucasian woman at 20 weeks' gestation. Labelled solid lines represent median values (in L/min for cardiac output, mL for stroke volume, dynes/sec/cm^5 for SVR) according to maternal height and weight, and unlabelled lines represent body mass indices of 18.5 kg/m^2 (blue line), 25 kg/m^2 (orange line) and 30 kg/m^2 (red line).

Figure 3. Estimated difference in median cardiac output (CO) (a) and SVR (b) according to maternal age relative to that at 25 years. Grey shaded area represents 95% CI.

Table 1. Demographic details of the study population

Parameter	Value
Maternal age (years)	32 (29-35)
Ethnicity	
Afrocaribbean	56 (13.6%)
Asian-South	31 (7.5%)
Asian-Other	24 (5.8%)
Caucasian	279 (67.9%)
Mixed/Other	20 (4.9%)
Not Stated	1 (0.2%)
Height (cm)	164 (160-169)
Weight at booking (kg)	64 (58-75)
Weight at examination (kg)	71 (63-83)
Mean arterial pressure (MAP) at booking (mmHg)	83 (78-89)
MAP at examination (mmHg)	84 (78-91)
Assisted conception	10 (2.4%)
Smoking at booking	20 (4.9%)
Nulliparous	219 (53.3%)
Gestational age at delivery (weeks)	40.0 (39.0-40.9)
Birthweight centile	45 (23-74)

Data are given as median (interquartile range) or *n* (%). MAP = mean arterial pressure.

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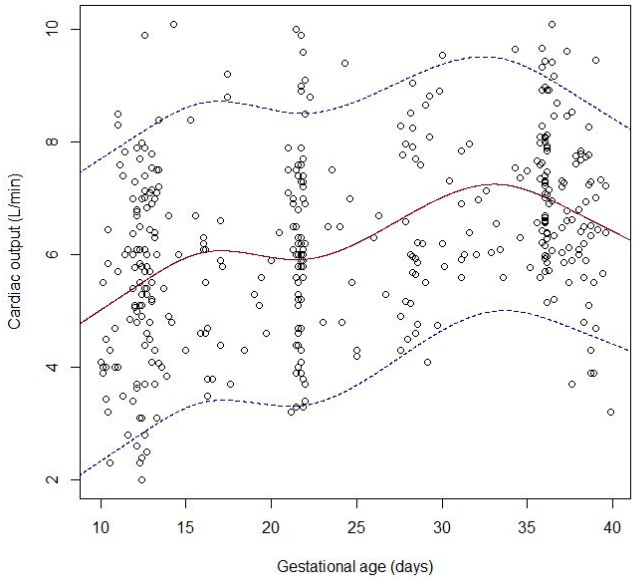
(a)



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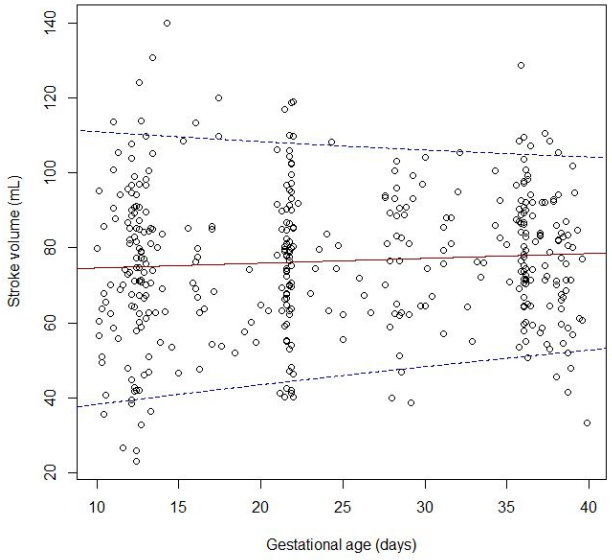

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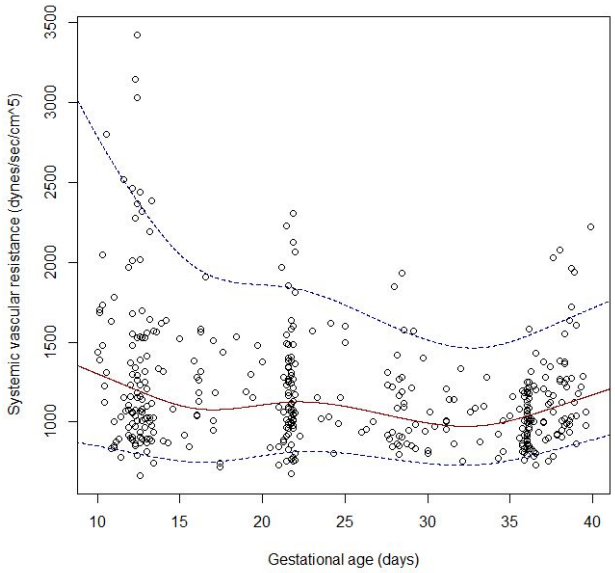

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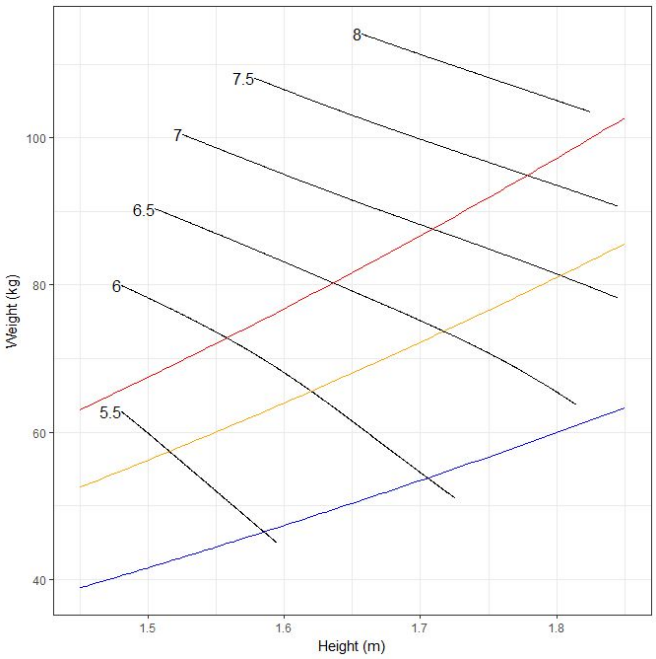
(a)



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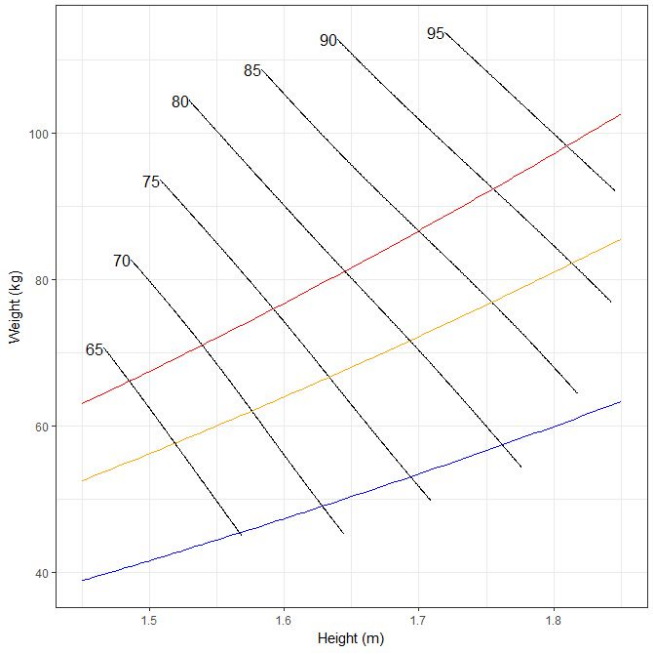

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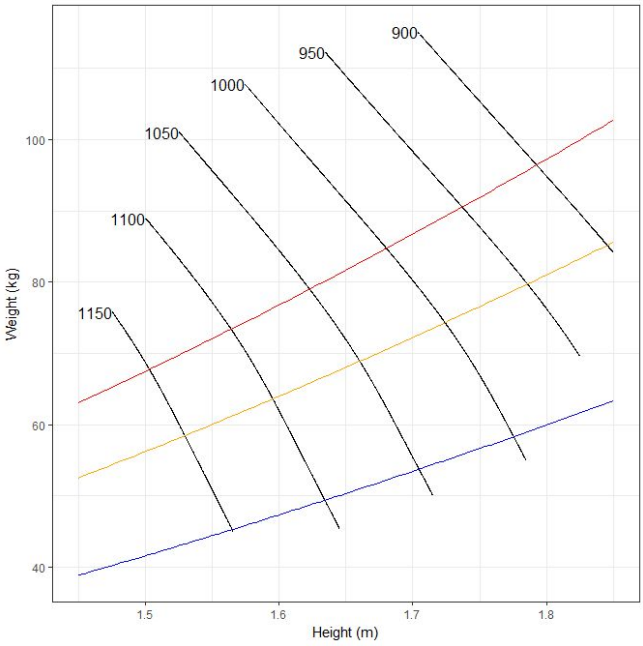

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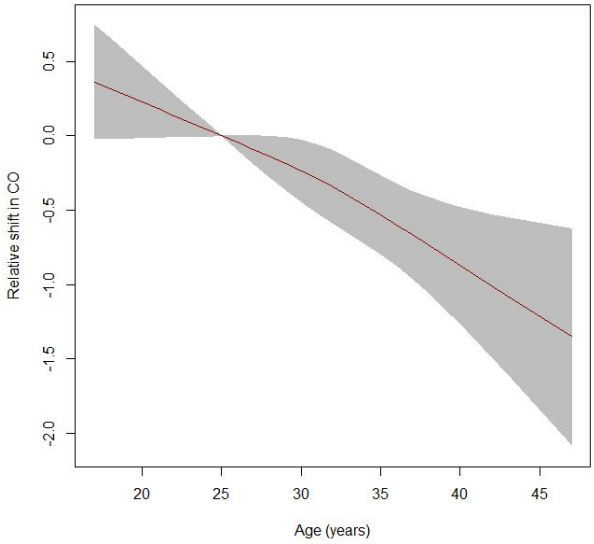

(b)