Birth weight and cardiac function assessed by echocardiography in adolescence: the Avon Longitudinal Study of Parents and Children

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Abstract

Objective: Maternal hemodynamics in pregnancy is associated with fetal growth and birth weight, which in turn is associated with offspring cardiovascular disease later in life. We therefore sought to quantify the extent to which birth weight is associated with cardiac structure and function in adolescence.

Methods: Participants (N=1,964, 55% females) from a UK birth cohort were examined with echocardiography at mean age 17.7 years (SD 0.3). Birth weight z-scores for sex and gestational age were used. Linear regression models were adjusted for several potential confounders, including maternal pre-pregnancy body mass index (BMI), maternal age, maternal level of education, and smoking during pregnancy.

Results: Higher birth weight was associated with lower E/A (mean difference -0.024, 95% confidence interval (CI); -0.043 to -0.005) and E/e' (-0.05; 95% CI -0.10; -0.0006) and also associated with higher left ventricular mass index (LVMI) (0.38 $g/m^{2.7}$; 95% CI 0.09; 0.67). There was no or inconsistent evidence of associations with relative wall thickness, left atrial diameter, and measurements of systolic function. Further analyses suggested that the association between birth weight and LVMI was mainly driven by an association observed in participants born small for gestational age and it was also abolished when risk factors in adolescence were accounted for.

Conclusions: Higher birth weight adjusted for sex and gestational age was associated with differences in measures of diastolic function in adolescence but the observed associations were small. It remains to be determined the extent to which these associations translate into increased susceptibility to cardiovascular disease later in life.

INTRODUCTION

Building on the initial work by Forsdahl[1] and Barker et al,[2] epidemiological and animal studies suggest that the intra-uterine environment and early life development are potentially important determinants of later cardiovascular disease (CVD).[3] For example, a hypoxic intra-uterine environment results in fetal growth restriction (FGR)[4] and lower birth weight, which might affect fetal cardiovascular development and increase the risk of CVD in adulthood.[5 6 7 8 9]

Studies in young children suggest that FGR, defined as being born small for gestational age (SGA) with additional evidence of placental dysfunction, is associated with altered cardiac development.[10 11] Similar, but more modest associations have been observed in those born SGA without evidence of placental dysfunction.[12 13 14 15] In adults, evidence of an association between birth weight and cardiac structure is contradictory or absent,[16 17 18] but most studies did not account for gestational age at birth,[18] or were restricted to those born at term.[17] Furthermore, there is an intricate relationship between fetal growth and cardiovascular hemodynamics[19] that might result in increased susceptibility to age-related risk factors such as blood pressure later in life. Studies on how fetal growth is associated with cardiac development between early childhood and middle age are thus needed. Myocardial differences observed in childhood could be abrogated in adulthood through compensatory mechanisms but still translate into worse CVD outcomes if the compensation is through tissue growth[20] at the expense of cardiac function.

In this study we aimed to investigate the association between birth weight (adjusted for sex and gestational age) and cardiac structure and function in adolescence. To do so, we focused on a set of complementary echocardiographic outcomes, each denoting different aspects of left atrial and ventricular structure and function in a birth cohort based in the UK.

METHODS

This study includes a subset of offspring from the Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective population-based birth cohort. Pregnant women resident in the county of Avon, United Kingdom, with expected dates of delivery between 1 April 1991 and 31 December 1992, were eligible for recruitment. Of 14,541 women originally recruited, there were 13,617 singleton offspring alive at age 1 year. In total, 4,770 of these participated in a clinic assessment at age 17 years and a random subsample were examined with echocardiography (N=1,980). Those with a successful examination, here defined as having an estimable ejection fraction, were included in the study sample (N=1,964, Figure 1). The study website contains details of all the data that are available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary/). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committee and informed consent was obtained from all participants.

Ascertainment of birth weight and co-variables

Data collection in ALSPAC has been described in detail for mothers[21] and offspring[22] elsewhere. In summary, data on birth weight, gestational age at birth, and maternal blood pressure, as well as urine dipstick measurements during pregnancy were abstracted from medical records by six trained midwifes. Here, birth weight was standardized as birth weight for gestational age by sex. To do so, we used an external and recently updated birth weight reference based on UK data from the same time period as the participants were born (early 1990s).[23] All mentions of birth weight below refer to sex and age specific birth weight z-score data. Additional information on data collection methods and definitions can be found in the Online Supplement.

Echocardiography examinations

The echocardiography examination protocol has previously been described.[24] One of two experienced echocardiographers performed the examinations following a standard protocol using an HDI 5000 ultrasound machine (Phillips) equipped with a P4-2 Phased Array ultrasound transducer. All measurements were performed according to American Society of Echocardiography guidelines. Based on

previous literature and to limit multiple comparisons, we focused on seven echocardiography measurements as outcomes; three principally as indicators of *cardiac structure* [Relative wall thickness (RWT), left ventricular mass indexed to height in $m^{2.7}$ (LVMI),[25] and left atrial diameter indexed to height in m (LADI)], two for *systolic function* [Ejection fraction and left ventricular wall velocity as measured with tissue doppler (s')], and two for *diastolic function* (E/A and E/e'). The echocardiography examinations are further described in the online supplement.

Statistical analyses

We first tested the extent to which modeling birth weight as a continuous variable was appropriate compared with different categorizations of birth weight that would allow for a non-linear association across birth weight distribution. To do so, we compared model fit statistics of a model with continuous birth weight with models including birth weight categorized in various ways for each echocardiography outcome (further described in Online Supplement).

In model I, we adjusted for sex and offspring age at the clinical assessment. In the main confounder adjusted model (Model II), we further adjusted for maternal height, maternal education, and pregnancy related factors; maternal age, parity, maternal pre-pregnancy body mass index (BMI), maternal diabetes during pregnancy, preterm birth, hypertensive disorders of pregnancy, and maternal smoking during pregnancy. These confounders were chosen a priori as variables that are plausible shared antecedent causes of the exposure (birth weight) and the cardiac outcomes. In model III, we further adjusted for participant factors in adolescence; BMI, systolic blood pressure (SBP), and heart rate. All variables additionally included in model III are potential mediators of the association between birth weight and cardiac outcomes. Consequently, the results of this model might be interpreted as indicating the effect of birth weight once the effects of birth weight acting through these mediators is accounted for; however mediation models have considerable potential to introduce other biases and the resulting model should be interpreted with caution and in the context of the assumptions made.[26]

We repeated all analyses in participants with complete data on birth weight and co-variables (N=1,592).

To test the extent to which any observed association was present also in those with normal birth weight,

we repeated the analyses but restricted the sample to those with a birth weight between the 10th and 90th percentile (thus excluding those with either small or large birth weight for gestational age and sex). To investigate the extent to which the indexing strategy influenced our results for LVMI and LADI, we performed complementary analyses in which we used different strategies to account for participant height (Online Supplement). We also performed interaction analyses by sex as there have been reports of different response to adverse fetal environment by sex.[27]

Multiple imputation

In total, 372 (19.9%) of included participants had missing data for either birth weight or other co-variables. To increase power and minimize bias, we used multiple imputation to impute missing values of birth weight and co-variables for all participants. All imputed variables had <10% missing data. We generated and analyzed 20 imputed datasets by implementing the mi impute and mi estimate commands in STATA 13.1 (StataCorp, College Station, TX, with further details provided in the Online Supplement). We imputed data for males and females separately to allow for testing of sex interactions in the imputed datasets.

RESULTS

Mean birth weight in our sample was 3.42 kg (SD: 0.52). Study sample characteristics compared to other singleton participants attending the age 17 years visit are shown in Table 1. Mean birth weight for gestational age and sex was similar between the two groups. Using model fit statistics, no strong evidence to suggest non-linearity in the associations between birth weight and outcomes was observed (Supplemental Results, Online Supplement).

Table 2 shows the linear association between birth weight and measures of cardiac structure and function in adolescence. In our main model, higher birth weight was associated with larger left ventricular mass (LVMI) and differences in diastolic function as assessed by E/A and E/e'. Adjustment for factors in adolescence (body mass index, systolic blood pressure, and heart rate) substantially attenuated the association between birth weight and LVMI and evidence of an inverse association with LADI emerged. There was no evidence of associations with RWT or ejection fraction.

Table 3 shows the associations between birth weight and echocardiography outcomes in participants with normal birth weight (between the 10^{th} and 90^{th} percentiles). Among these participants, there was no evidence of an association between birth weight and LVMI. However, the estimates of inverse associations with diastolic function (E/A and E/e') were similar to those observed in the main analysis. To explore these findings further, we generated linear splines with knots at the 10^{th} and 90^{th} percentile of birth weight for gestational age (method further described in Online Supplement). This analysis revealed a positive association between birth weight and LVMI (mean difference: 2.44, 95 % CI 0.89; 4.00) that was restricted to participants with low birth weight (z-score $<10^{th}$ percentile). In the complementary analyses on the handling of height the results for left ventricular mass remained similar, while the associations for left atrial size appeared somewhat strengthened in model II (Supplemental Results, Online Supplement). We did not observe any strong evidence of interaction by sex for any outcome (data not shown). The most discordant analyses by sex were the association between birth weight and s', for which we observed an association in females (mean difference 0.10, 95% CI 0.01; 0.20) but not in males (-0.01, -0.11; 0.10, p=0.06 for interaction).

DISCUSSION

In this study we found higher birth weight by sex and gestational age to be associated with measures of cardiac diastolic function in late adolescence. We also observed a positive linear association between birth weight and LVMI but this appeared to be driven by participants born SGA. The observed effect sizes are small – corresponding to roughly 1-2% of the mean echocardiography measurement in the sample per one SD birth weight – and should not have clinical relevance in young adulthood. However, the novelty and potential clinical implications of our results might be best understood if viewed from a life course perspective. During gestation and throughout life, cardiac and vascular structures develop and function interdependently. Verburg et al reported that FGR, defined by ultrasound and placental function, is associated with adaptive cardiovascular changes in the fetus.[27] Furthermore, the number of cardiomyocytes at birth appears to determine the number of cells later in life.[20] Subsequent growth of the tissue is mostly mediated through increased cellular size and not numbers. Thus, the trajectories of cardiac growth and development over the life course might be dependent on prenatal factors that are reflected in birth weight. In middle age, greater left ventricular mass is a risk factor for coronary heart disease[28] and larger left ventricular mass in older adults is associated with developing reduced ventricular function.[29] Consequently, a model of increased susceptibility with age in those with low birth weight might be accurate; the first insult of reduced fetal growth results in suboptimal myocardial development, which translates into increased susceptibility to age-related increase in afterload[30] and CVD risk factor burden. Another potential explanation for our results is that there are pleiotropic genetic effects that influence both fetal growth and cardiac structure and function. Investigations on the extent to which trajectories of cardiac remodeling across the life course differ by birth weight status are needed and would add substantially to our understanding of cardiac development and adaptation.

Crispi et al[10] and Sarvari et al[11] reported FGR (defined as low birth weight and evidence of placental dysfunction) to be associated with more globular shape in pre-school children and pre-adolescents. Geelhoed et al[15] reported that higher birth weight was associated with higher left ventricular mass at two years while Hietalampi et al[14] observed an association between birth weight and left ventricular mass at

age 15 years. Although we in this study initially found support for a similar association, further analyses suggested that the association between birth weight and LVMI was restricted to participants born SGA. Birth weight is associated with later blood pressure,[31] BMI,[32] and heart rate[33] and we considered these variables as potential mediators in the analyses. Still, only the effect estimates for LVMI and LADI appeared quantitatively different in the model that included these mediators in adolescence (model III) compared to our main confounder-adjusted model (model II). These differences could potentially be explained by a large proportion of the association being mediated by the variables additionally included, or the presence of collider-stratification bias.[26]

This study also suggests that larger birth weight might be associated with relatively smaller left atrial size. Though this observation was dependent on the handling of height in the models, the most plausible models all supported an association. A larger left atrial size in general is associated with increased risk of atrial fibrillation[34] and CVD events[35] in adults. However, there is conflicting evidence of the association between birth weight and atrial fibrillation,[36] and the use of crude birth weight without adjusting for GA and the potential for adult height to mediate some of the effect further contributes to the difficult interpretation of these studies.

E/e' correlates with the left ventricular diastolic filling pressure (in general lower is better), predicts cardiac events among patients with hypertension,[37] and is one of several measurements recommended to evaluate diastolic dysfunction in heart failure diagnosis,[38] although its validity as a measure of left atrial filling pressure in healthy individuals is controversial.[39] Crispi et al reported that FGR was associated with smaller s' and larger E/e' in children age 5 years,[10] with similar but attenuated association observed in offspring born SGA.[12] Our results suggest that in ALSPAC altered diastolic function is not isolated to those born with smaller birth weight, but that there is a negative association between birth weight and diastolic function across the birth weight distribution. s', a sensitive marker of systolic left ventricular function, is negatively associated with risk of heart failure and cardiovascular death independently of classical cardiovascular risk factors.[40] In this study, we observed a tendency of interaction between sex and birth weight for the association with s', with a positive association observed only in females. As the

support for an interaction is weak and multiple outcomes were tested for interactions, this might very well be a chance finding. In fact, previous studies have reported no difference in association between FGR and lower s' by sex.[10 11]

When compared to previous studies, the novelty and methodological strengths of this study are the combination of well-defined maternal pregnancy data that allow for better control of confounding, the prospective longitudinal cohort study approach, the duration of follow-up until adolescence, and the use of multiple imputation to address missing data. However, the study also has some relevant limitations. Only a subset of the original birth cohort was examined with echocardiography at typically age 17 years, though a pseudorandom sample was chosen among adolescents attending the follow-up at the time and the birth weight z-score, SBP, and BMI were similar in in the study sample compared to all examined adolescents. In addition, we had no data on placental dysfunction. Hence, our ability to distinguish reduced fetal growth from non-pathological small birth weight had limitations. Furthermore, it should be noted that there are inherent limitations with utilizing estimates of cardiac volumes from 2-dimensional imaging data. For example, it has previously been reported that the FGR is associated with left ventricular shape.[10 11] This might affect the geometrical assumptions made when estimating LVMI.[10] Still, our observations for LVMI appeared to be robust across different strategies of accounting for adolescent body size.

In conclusion, higher birth weight across the entire range was associated with minor alterations in diastolic function in adolescence as measured by echocardiographic indicators. By contrast, the positive association between birth weight and LVMI was driven by those born SGA. All observed effect estimates were small but should be considered in the perspective of life course trajectories. If, and the extent to which, these associations are explained by causal effects mediated through birth weight, pleiotropic genes, or suboptimal maternal cardiovascular adaptation to pregnancy[41] remains to be elucidated.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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Figure legend

Figure 1 – Identification of the study sample

Table 1 – Characteristics of study sample (N=1,964) compared to other singleton participants attending the age 17 years clinical assessment (N=2,806)

	Study sample	N with data	Attended the age 17 clinical assessment but not in sample	N with data
Measurements related to birth and maternal pregnancy				
Female, % (N)	55.0 (1,080)	1,964	56.9 (1,596)	2,806
Birth weight, kg Mean (SD)	3.42 (0.52)	1,940	3.44 (0.53)	2,777
Birth weight z-score, Mean (SD)	0.12 (1.00)	1,940	0.15 (1.09)	2,776
Maternal age at delivery, years Mean (SD)	29.4 (4.6)	1,964	29.0 (4.7)	2,806
Maternal height, meters Mean (SD)	1.64 (0.07)	1,868	1.64 (0.07)	2,661
Maternal pre-pregnancy BMI, kg/m^2 Median (IQR)	22.2 (20.5–24.4)	1,776	22.0 (20.5–24.2)	2,554
First pregnancy, % (N)	50.0 (955)	1,911	47.0 (1,268)	2,701
Preterm birth (<37 gestational weeks), % (N)	4.3 (85)	1,964	4.5 (126)	2,806
Diabetes or glycosuria during pregnancy, % (N)	3.6 (68)	1,890	4.5 (121)	2,693
Maternal HDP or hypertension, % (N)		1,870		2,676
- No HDP or hypertension	78.8 (1,474)		79.9 (2,139)	
- Gestational hypertension	15.7 (294)		14.2 (379)	
- Preeclampsia	2.6 (49)		2.2 (58)	
- Essential hypertension	2.8 (53)		3.7 (100)	
Maternal smoking status during pregnancy, % (N)		1,928		2,746
- Never smoked	79.2 (1,527)		75.3 (2,068)	
- Stopped prior the second trimester	9.0 (173)		11.4 (313)	
- Smoked during the second trimester	11.8 (228)		13.3 (365)	
Maternal educational level, % (N)		1,906		2,698
- Compulsory/Vocational	19.7 (375)		19.3 (521)	
- Compulsory (higher achievement)	33.4 (637)		34.6 (934)	
- Secondary (academic preparation)	26.7 (508)		28.5 (769)	
- Tertiary/Degree	20.3 (386)		17.6 (474)	
Measurements from the 17 years follow-up				
Age, years Mean (SD)	17.7 (0.3)	1,964	17.9 (0.5)	2,806
BMI, kg/m^2 Median (IQR)	21.9 (20.1-24.7)	1,929	21.9 (20.1-24.5)	2,703
Heart rate, beats/minute Mean (SD)	64 (10)	1,905	65 (10)	2,392
Systolic blood pressure, mmHg Mean (SD)	119 (11)	1,905	118 (11)	2,392
Diastolic blood pressure, mmHg Mean (SD)	64 (6)	1,905	64 (7)	2,392
Cardiac structure				
LVMI, g/m$^{2.7}$ Mean (SD)	28.9 (6.2)	1,929		
LADI, cm/m Mean (SD)	1.86 (0.23)	1,730		
Relative wall thickness, Mean (SD)	0.38 (0.06)	1,963		
Systolic Function				
Ejection fraction, % Mean (SD)	66.8 (6.4)	1,964		
Average s', cm/s Mean (SD)	7.8 (1.4)	1,881		
Diastolic function				
E/A ratio, Mean (SD)	1.93 (0.40)	1,895		
E/e' ratio, Mean (SD)	4.9 (1.0)	1,878		

ALSPAC: Avon longitudinal study of parents and children, BMI: Body mass index, HDP: Hypertensive disorders of pregnancy, LADI: Left atrial diameter indexed to height in m, LVMI: Left ventricular mass indexed to height in m$^{2.7}$

Table 2 – The association between birth weight and cardiac structure and function in adolescence

	Model	*Difference per 1 SD in birth weight* (95% CI)*
Cardiac structure		
Left ventricular mass index, g/m$^{2.7}$	I	0.38 (0.11, 0.66)
(N=1,929)	II	0.38 (0.09, 0.67)
	III	0.08 (-0.17, 0.32)
Left atrial diameter index, cm/m	I	-0.002 (-0.013, 0.009)
(N=1,730)	II	-0.007 (-0.018, 0.005)
	III	-0.017 (-0.028, -0.007)
Relative wall thickness	I	0.001 (-0.002, 0.003)
(N=1,963)	II	0.001 (-0.001, 0.004)
	III	0.001 (-0.002, 0.004)
Systolic function		
Ejection fraction, %	I	-0.22 (-0.50, 0.06)
(N=1,964)	II	-0.23 (-0.53, 0.07)
	III	-0.20 (-0.50, 0.10)
s’	I	0.06 (-0.0003, 0.13)
(N=1,881)	II	0.05 (-0.02, 0.12)
	III	0.05 (-0.02, 0.12)
Diastolic function		
E/A ratio	I	-0.028 (-0.046, -0.010)
(N=1,895)	II	-0.024 (-0.043, -0.005)
	III	-0.026 (-0.045, -0.007)
E/e’ ratio	I	-0.06 (-0.10, -0.01)
(N=1,878)	II	-0.05 (-0.10, -0.001)
	III	-0.04 (-0.09, 0.01)

CI: Confidence Interval; SD: Standard deviation
Birth weight is modelled as standardized birth weight per gestational week and sex.
Model I: adjusted for age at examination and sex (male or female)
Model II: additionally adjusted for: maternal height, maternal hypertensive disorders of pregnancy (preeclampsia, gestational hypertension, essential hypertension, or none), maternal age at pregnancy, maternal BMI, maternal parity (parous or nulliparous), maternal smoking during pregnancy (never, stopped prior second semester, smoked during the second semester), maternal education (compulsory/vocational, compulsory/higher achievement, secondary/academic preparation, or tertiary/degree), maternal diabetes mellitus during pregnancy (yes or no), and preterm birth (<37 weeks, yes or no)
Model III: additionally adjusted for factors in adolescence: body mass index, systolic blood pressure, and heart rate
* 1 SD roughly corresponds to 0.45 kg at gestational week 40.

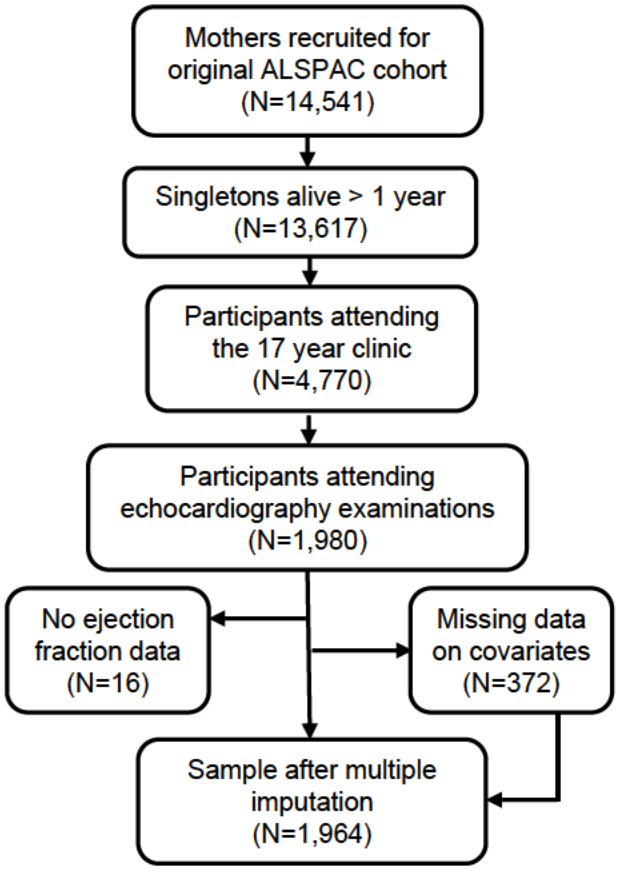
Table 3 – The association between birth weight and cardiac structure and function in participants with normal birth weight

	Difference per 1 SD in birth weight* (95% CI)
Cardiac structure	
Left ventricular mass index, g/m$^{2.7}$	0.01 (-0.45, 0.48)
Left atrial diameter index, cm/m	-0.007 (-0.026, 0.012)
Relative wall thickness	-0.0002 (-0.005, 0.004)
Systolic function	
Ejection fraction, %	-0.45 (-0.93, 0.03)
s'	0.11 (-0.004, 0.22)
Diastolic function	
E/A ratio	-0.03 (-0.07, -0.003)
E/e' ratio	-0.08 (-0.16, -0.001)

Birth weight is modelled as standardized birth weight per gestational week and sex. Normal birth weight is defined as birth weight z-score corresponding to the 10th to 90th percentile. The number of participants with available outcome data varies by echocardiographic measurement. In addition, there is a small proportion of imputed birth weight data resulting in potentially different N in each imputed dataset.

Models (II) adjusted for age at examination, sex (male or female), maternal height, maternal hypertensive disorders of pregnancy (preeclampsia, gestational hypertension, essential hypertension, or none), maternal age at pregnancy, maternal BMI, maternal parity (parous or nulliparous), maternal smoking during pregnancy (never, stopped prior second semester, smoked during the second semester), maternal education (compulsory/vocational, compulsory/higher achievement, secondary/academic preparation, or tertiary/degree), maternal diabetes mellitus/glycosuria during pregnancy (yes or no), and preterm birth (<37 weeks, yes or no)

* 1 SD roughly corresponds to 0.45 kg at gestational week 40.


Mothers recruited for original ALSPAC cohort (N=14,541)
Singletons alive > 1 year (N=13,617)
Participants attending the 17 year clinic (N=4,770)
Participants attending echocardiography examinations (N=1,980)
No ejection fraction data (N=16)
Missing data on covariates (N=372)
Sample after multiple imputation (N=1,964)