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The relationship between umbilical cord length and chronic rheumatic heart disease: a prospective cohort study

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Abstract

Background: One previous, preliminary study reported that the length of the umbilical cord at birth is related to the risk of developing chronic rheumatic heart disease in later life. We sought to replicate this finding.

Design: Prospective, population-based birth cohort.

Methods: We traced 11,580 individuals born between 1915 and 1929 in Uppsala, Sweden. We identified cases with a main or secondary diagnosis of chronic rheumatic heart disease in the Swedish national inpatient, outpatient or death registers. Archived obstetric records provided data on umbilical cord length, gestational age, birthweight and placental weight.

Results: There were 136 patients with chronic rheumatic heart disease (72 men and 64 women) with a mean age at first hospital admission of 68 years (range 36-92). There was evidence of a positive association between umbilical cord length and risk of subsequent chronic rheumatic heart disease. The overall hazard ratio in the Swedish study (HR 1.13, 95%CI 1.01 to 1.27) was similar to that of the previous study, with some suggestion of larger effect in men than in women. No other birth characteristics were predictive except for weak evidence of a negative effect of birthweight.

Conclusions: People with longer umbilical cords at birth are more likely to develop chronic rheumatic heart disease in later life. As longer umbilical cords have more spiral arteries and a higher vascular resistance, we hypothesize that the increased pressure load on the heart leads to changes in endothelial biology and increased vulnerability to the autoimmune process initiated by infection with β -haemolytic streptococci.

Keywords: Rheumatic heart disease; umbilical cord; birthweight; fetal programming; developmental origins of health and disease

Introduction

Although now rare in the Western world, chronic rheumatic heart disease remains one of the most important causes of morbidity and mortality from heart disease in many developing countries.¹ It is well established that infection with group-A β -haemolytic streptococci plays a pathogenic role in precipitating rheumatic fever and triggering the autoimmune process which culminates in valvular heart disease. Nevertheless, only a relatively small proportion of those infected with rheumogenic streptococci actually go on to develop rheumatic fever and its subsequent cardiac complications.² The reasons for this susceptibility, which may be as low as 3 to 6%, include variations in the virulence of the causative group A streptococcus and genetic differences in host susceptibility. These two factors cannot, however, fully explain the epidemiology of the disease.

It is now widely accepted that birth outcomes such as low birthweight and preterm birth are associated with subsequent cardiovascular risk³ and cardiovascular outcomes.⁴ We have hypothesised that differences in maternal characteristics and in the prenatal environment may also increase risk by influencing the abnormal response to infection with group A streptococcus. This is supported by both animal and human evidence, which indicates that such factors can influence the immune response⁵ and vascular endothelial function.⁶ In a study carried out in the Helsinki Birth Cohort Study, which comprises over 20,000 men and women born 1924-1944, we identified 101 people who were admitted to hospital or who had died from chronic rheumatic heart disease. The disease was not associated with body or placental size at birth. An unexpected finding, however, was that the disease was associated with a long umbilical cord such that the hazard ratio for the disease was increased by 23% for every 10 cm increase in cord length.⁷ In this paper, we therefore seek to replicate these findings from Finland in a second, independent cohort from Sweden.

Methods

Sample selection

The Uppsala Birth Cohort Study (UBCoS) comprises all live births at the Uppsala University Hospital between 1915 and 1929.⁸ This hospital delivered an estimated 75% of births in Uppsala city and 50% of births in surrounding rural parishes. The birth cohort is representative of Sweden nationally in terms of infant mortality and fertility,⁹ albeit with a somewhat higher proportion of infants from urban areas.¹⁰ From a total of 13,748 singleton births, 13,383 (97%) were successfully traced through parish archives until death, emigration or until being assigned a unique personal number in 1947. Of these, we excluded 1703 who died and 100 who emigrated before 1964, when hospitalisation information first became available. Our study population therefore comprised 11,580 individuals (48% female) who were followed up from 1964 to end 2008. Ethical approval for the UBCoS study was granted by the Regional Ethics committee in Stockholm (dnr 03-117, dnr 04-944T and dnr 2009/1115-32), and this study conforms to the ethical guidelines of the Declaration of Helsinki.

Chronic rheumatic heart disease outcome

Cases were defined using the International Classification of Diseases (ICD) codes 410-414 (revision 7), codes 393-398 (revisions 8 and 9) and codes I05-I09 (revision 10). Of these, the mitral cases have ICD codes 410, 394 and I05, and the aortic cases have codes 411, 395 and I06. We identified cases as individuals with a main or secondary diagnosis of chronic rheumatic heart disease in the Swedish national inpatient, outpatient or death registers. The inpatient register is available but incomplete in the Uppsala region from 1964 and is complete in the region from 1970.¹¹ Other areas of Sweden took somewhat longer to start and to complete the registration of inpatient hospitalisations. The outpatient register is only available from 2001 and is largely limited to public facilities, whereas the inpatient register covers both public and private facilities.¹¹

Cord length and other explanatory variables

Archived obstetric records provided data on the length of cohort members' umbilical cords, and also on their gestational age, birthweight and placental weight. These records also provided information on cohort members' parents, including mother's age, mother's marital status and the occupational social class of the head of the household (categorised as in Table 1). For the 3% of cohort members missing occupational social class data in the obstetric records, we instead sought to use data from siblings, subsequent school records or the 1930 census.¹⁰ Adult socio-economic position was measured using (i) the highest educational level recorded in any census (1960-1990), and (ii) an indicator of 'crowding' from the 1960 census, defined as having more than two occupants per bedroom. Our findings were unchanged when using additional or alternative indicators such as occupational social class in 1960, indicators which we did not use in the main analysis because of higher missing data.

Statistical methods

We used Cox regression to calculate hazard ratios, starting follow-up on 1st January 1964 and continuing until 31st December 2008 or until death, emigration or first diagnosis for chronic rheumatic heart disease, whichever was earliest. The percentage of missing data ranged from 0-3% across our explanatory variables, including 0.6% for umbilical cord length. We used multiple imputation (twenty-five imputations) to impute these data under an assumption of missing at random, including in our imputation model event indicators for the outcome and the Nelson-Aalen estimator of cumulative hazard.¹² We entered continuous variables as linear terms because entering quadratic terms never provided evidence of non-linearity (all $p > 0.05$), and we used robust standard errors to allow for potential correlations between children born to the same mother. We tested *a priori* for interactions with sex.

Table 1: Characteristics of study population (N=11,580)

			N	% / mean (SD)
Sex & birth year	Sex	Female	5562	48%
		Male	6018	52%
year	Birth year	1915-1919	3019	26%
		1920-1924	3941	34%
		1925-1929	4620	40%
Birth characteristics	Umbilical cord length (cm)		11506	57.7 (13.3)
	Gestational age (completed weeks)		11193	39.5 (2.1)
	Birthweight (g)		11500	3462 (505)
	Placental weight (g)		11503	662 (140)
	Head circumference (cm)		11262	34.8 (1.5)
Social characteristics	Mother's age at child's birth (years)		11578	28.4 (6.5)
	Mother unmarried	No	9232	80%
		Yes	2324	20%
	Parent's social class at cohort member's birth	High/med. non-man.	1010	9%
		Self-empl. & farmers	2156	19%
		Lower non-manual	819	7%
		Skilled manual	1719	15%
		Unskilled manual	5676	50%
	Crowded housing, 1960	No	9877	88%
		Yes	1396	12%
	Highest education level, 1960-1990	Primary, ≤8 years	6285	54%
Primary, 9-10 years		742	6%	
Higher secondary		3252	28%	
Tertiary, < 3 years		482	4%	
	Tertiary, ≥ 3 years	793	7%	

SD, standard deviation; High/med. non-man., high/mediate non-manual; self-empl., self-employed. Numbers add to less than 11,580 for some variables because of missing data. Correlations between variables were all $r < 0.7$ and most $r < 0.3$

We then created forest plots to compare our findings to those of the previous Finnish study.⁷ In these we used random effects meta-analysis to estimate an overall pooled effect size across the difference studies.¹³ We also present I^2 values, a statistic that indicates the proportion of variation between studies that is estimated to be attributable to underlying heterogeneity in effect sizes across the study populations, as opposed to just random error.¹³ All analyses used Stata 12.

Results

There were 136 patients with chronic rheumatic heart disease (overall rate 322 per million person years), 72 men (rate 345 per million) and 64 women (rate 300 per million). Of these patients, 103 were ascertained through the inpatient register, 12 through the outpatient register and 21 through the death register. The mean duration of follow-up was 36.4 years, and the mean age of patients at first hospital admission was 67.7 years (range 36-92). When first diagnosed with chronic rheumatic heart disease, the mitral valve was affected in 52 of the cases, the aortic valve in 54 and both valves in a

further 9. In the remaining 21 cases the disease had affected other endocardial structures or the pericardium or was unspecified.

Rates of the disease fell progressively among those cohort members who were born more recently ($p=0.02$), with rates of 534 per million in people born during 1915-1919, 332 per million in people born during 1920-1924, and 199 per million in people born during 1925-1929. This downward trend in the rates over time was also observed in the Finnish study, and meant that overall the rate in our study population (born 1915-1929) was higher than in the younger Finnish population (born 1924-1944). Nevertheless, for those birth years of overlap between the two samples, rates in our subjects appeared lower than in Finland (199 per million in our study among those born 1925-1929 versus 348 per million among those born 1924-1928 in the Finnish sample).⁷

Association between umbilical cord length and rheumatic heart disease

Umbilical cord length was greater in males than females (58.8 vs. 56.6 cm, $p<0.001$), and was also weakly positively associated with socio-economic advantage ($r=0.03$, $p=0.003$). Cord length was also positively associated with gestational age ($r=0.08$, $p<0.001$), birthweight ($r=0.20$, $p<0.001$) and placental weight ($r=0.24$, $p<0.001$). Apart from a weak negative association with birthweight, which was only statistically significant after adjustment, umbilical cord length was distinctive among the birth characteristics in being the only one to show any strong evidence of an association with subsequent risk of chronic rheumatic heart disease. Specifically, longer umbilical cord length predicted a higher rate of the disease in men but showed no evidence of an association in women (

Table 2, $p=0.05$ for sex interaction in both univariable and adjusted analyses). Chronic rheumatic heart disease was not related to the parents' social class at birth or the individual's subsequent social position as indicated by level of education or household crowding.

We repeated the analyses presented in

Table 2 limiting our outcome to cases of chronic rheumatic heart diseases affecting (i) the mitral valve and (ii) the aortic valve. Both were positively and significantly associated with umbilical cord length in men, but there was a trend towards a larger association with diseases of the mitral valve (adjusted HR 1.39, 95%CI 1.16, 1.68 per 10cm increase for disease of the mitral valve; HR 1.25, 95% CI 1.04, 1.50 for disease of the aortic valve). Neither of these outcomes was associated with umbilical cord length in women (both $p > 0.2$ in adjusted analyses).

Table 2: Hazard ratios for association between birth characteristics and chronic rheumatic heart disease

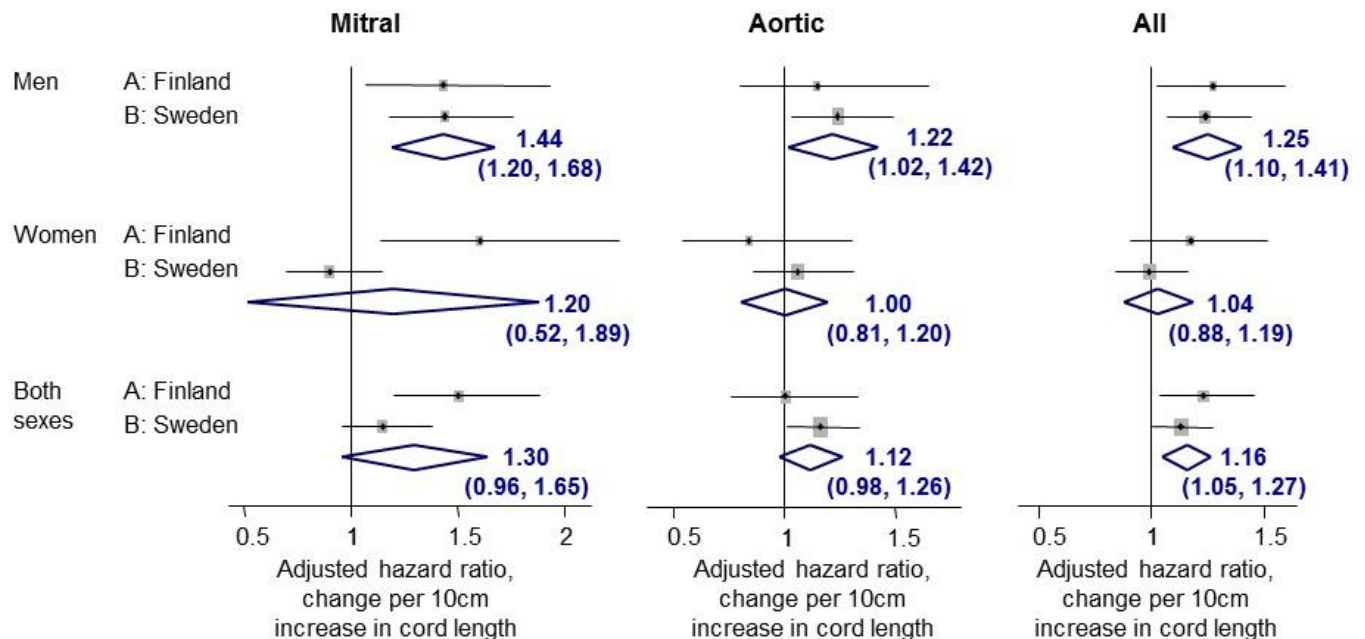
	Men (N=6018)		Women (N=5562)	
	Minimally-adjusted HR (95%CI)	Adjusted HR (95%CI)	Minimally-adjusted HR (95%CI)	Adjusted HR (95%CI)
Umbilical cord length (change per 10cm)	1.24 (1.07, 1.44)**	1.23 (1.06, 1.43)**	0.99 (0.84, 1.16)	0.99 (0.85, 1.17)
Gestational age (change per week)	1.01 (0.89, 1.13)	1.04 (0.92, 1.17)	0.97 (0.88, 1.08)	0.98 (0.88, 1.10)
Birthweight (change per 100g)	0.97 (0.93, 1.02)	0.91 (0.85, 0.98)*	1.00 (0.96, 1.04)	1.03 (0.97, 1.10)
Placental weight (change per 100g)	1.06 (0.90, 1.26)	1.12 (0.93, 1.34)	1.02 (0.88, 1.20)	1.04 (0.86, 1.24)

* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$. HR, hazard ratio; CI, confidence interval. Minimally-adjusted analyses adjust for birth year only, adjusted analyses additionally include all variables in the column plus mother's age, marital status, parent social class, cohort member's education and crowded housing.

Comparison of Swedish and Finnish results

Figure 1 presents a meta-analysis combining the results of this Swedish study with the previously-published Finnish study. It presents minimally-adjusted analyses, as these are what have previously been published in the Finnish study⁷ and as adjustment for social or biological characteristics had very little effect in the present study. The overall hazard ratio in the Swedish study (HR 1.13, 95%CI 1.01, 1.27) was similar to that of the Finnish study (1.23, 95%CI 1.04, 1.45). Likewise both studies show similar risks in men with increasing cord length, while the risks in women were non-significant. In both sexes, the effect of cord length was greater in cases affecting the mitral than the aortic valve. However, this difference between these two disease sites was only significant in the Finnish study.

Figure 1: Random-effects meta-analysis for the adjusted association between umbilical cord length and hazard ratio for chronic rheumatic heart disease



Study A is the birth cohort in Helsinki, Finland (N=20,431, born 1924-1944); Study B is the birth cohort in Uppsala, Sweden (N=11,580, born 1915-1929). Both sets of analyses adjusted for year of birth and sex. All $p > 0.05$ for heterogeneity between men and women, except mitral cases in females ($I^2=0.81$, $p=0.02$)

Discussion

This study replicates our previous finding of a positive association between a longer umbilical cord at birth and the risk of chronic rheumatic heart disease in adult life. Comparison of the present results with the previous Finnish study⁷ shows consistent evidence of an effect across the two studies. There was also a trend in both studies for a larger effect in men than in women (although this difference was only significant in Sweden), and for a stronger effect in mitral cases than in aortic cases (although this difference was only significant in Finland).

Study limitations

Like the previous Finnish study,⁷ the present study was based on people who were either hospitalised or died from rheumatic heart disease. The hospital data included people who were either inpatients or outpatients with a main or secondary diagnosis, from hospital registers which have high validity relative to more detailed diagnostic techniques (positive predictive values 82%-100% across five studies examining heart disease).¹¹ We will, however, have missed any people with subclinical or mild disease who had not been referred to the hospital system. We also lacked information on hospitalisations prior to 1964, when our cohort members were aged 35-50 years, and for some years after 1964 information on hospitalisations was not complete.

As for the validity of our primary exposure, umbilical cord length, this showed plausible patterns of association with birthweight and gestational age but is nonetheless likely to be subject to some measurement error by the hospital midwives. Both for this exposure and for our heart disease outcome, we have no reason to believe that errors are likely to be differential with respect to our primary hypothesis. As such, any effect of this measurement error is likely to have been such as to underestimate the magnitude of the association between umbilical cord length and rheumatic heart disease.

A final important limitation is that the number of cases in each study was relatively small, which complicates interpretation of the apparent differences between the studies. For example, with regard to the consistent trend towards a larger effect of cord length in men than in women, it is unclear whether this trend was not significant in Finland because of low power or whether it was borderline significant in Sweden because of chance.

Potential mechanisms of the effect

Although rheumatic fever and rheumatic carditis occur as a sequel to β -haemolytic streptococcal infection, the pathogenesis of rheumatic fever is poorly understood. Previously it has been thought that this involves cross reactivity between components of the causative streptococcus and sarcomeric proteins. However, this hypothesis does not explain many of the features of the disease such as multisystem involvement, the sparing of the myocardium and the specific effects on valvular tissue.¹⁴ Recent studies suggest that surface components of rheumogenic streptococcal strains form a complex with human collagen type IV in subendothelial basement membranes which might initiate an autoantibody response to collagen.^{15, 16} Furthermore, one of the striking features of rheumatic fever is that, despite the widespread endothelial activation and diffuse collagen involvement of the vasculature and myocardium, the long term effects are confined almost exclusively to the cardiac valves. It has been suggested, therefore, that whereas endothelial lesions elsewhere are able to heal without scarring, the unique structure of the cardiac valves, which consist of a thin layer of connective tissue covered with epithelium without muscular tissue or blood vessels, make them susceptible to a vicious cycle of inflammation, angiogenesis and progressive scarring.¹⁴ There is good evidence that the size, shape, thickness and nuclear orientation of endothelial cells varies according to their anatomical site in the body.¹⁷ These differences are even observed within the heart, for example in differences between endothelial cells lining the pulmonary artery versus those lining the aorta. Both the microscopic and ultrastructural morphology of these cells appear to be responsive to local environmental factors such as shear stress.¹⁸ These differences are paralleled by differences in transcription factor expression¹⁹ and are even specific to the particular parts of the valve: endothelial cells on the aortic side of the aortic valve have different microarray expression profiles from those on the ventricular side.²⁰ There is also increasing evidence that these differences in endothelial cell biology have a developmental origin and are linked with epigenetic modification.¹⁷ For example, DNA microarray studies of multiply passaged endothelial cells cultured from different anatomical sites reveal different transcriptional profiles, and provide compelling evidence for epigenetic modification.

It is conceivable, therefore, that the effect of a long umbilical cord on the risk of chronic rheumatic heart disease could be mediated by influencing the endothelial response to autoimmune-mediated injury and the extent to which chronic inflammation of the valves progresses to scarring and clinically evident heart disease. The umbilical arteries spiral around the central umbilical vein. A longer cord will have increased spiralling, and this will increase the resistance to flow and the pressure load on the fetal heart. Longer umbilical cord length therefore increases systolic load in the fetus, and there is evidence that increased systolic pressure affects cardiac remodelling in the developing heart.²¹ For example, an increase in systolic load will stimulate cardiac growth both by hyperplasia and hypertrophy and will stimulate maturation and binucleation of the cardiomyocytes.²² Interestingly, increased umbilical artery resistance is also observed in fetal growth restriction,²³ and this is consistent with our finding that lower birthweight also predicted rheumatic heart disease in multivariable analyses.

The suggestion of sex differences that we have observed could also be consistent with this proposed mechanism. Considerable evidence indicates that endothelial dysfunction is more prevalent in men than women, and this may contribute to their higher prevalence of cardiovascular disease.²⁴ These endothelial differences are thought to result from the influence of sex steroids which affect a wide variety of cellular processes including vascular repair after injury. Additionally or alternatively, there also exist sex-related differences in phosphoprotein signalling in response to elevated hemodynamic stress within valvular structures associated with umbilical cord length. Evidence from rat studies indicates that, following intrauterine exposure to hypoxia, the promoter region of the protein kinase C-epsilon (PKC ϵ) gene is methylated to a greater extent in males than in females.²⁵ This lower level of PKC ϵ promoter methylation in females seems to reflect the action of estrogen,²⁵ and it is possible that a similar process may operate in human cardiac valves. The expression of PKC enzymes appears important in the aetiology of heart disease, including evidence that PKC isoforms are differentially regulated in abnormal bicuspid aortic valves²⁶ and that PKC ϵ appears to protect human vascular endothelium against the deleterious effects of endothelin-1.²⁷ It is therefore possible that estrogen suppresses methylation of PKC isoforms during the formative stages of the valve, and that this offers protection against hemodynamic stress.

Finally, in Finland cord length was much more strongly linked to rheumatic heart disease affecting the mitral than the aortic valve. This finding was, however, less evident in the current study. The combined analysis (Figure 1) suggested a somewhat greater effect on the mitral than the aortic valve (HR 1.30 vs. 1.12), but the difference was not significant. These data are limited by the fact that diagnoses were made clinically, and thus subject to misclassification errors: indeed, histopathological analysis from autopsies of cases of rheumatic heart disease show that the mitral valve is almost always affected and that the aortic valve is frequently inflamed.²⁸ Nevertheless, if it is the case that the mitral valve shows greater susceptibility to the effects of long cord length, a possible explanation is that the mitral leaflets are larger and have greater wall stress.

Conclusion

In summary, we have replicated our finding that men who have longer umbilical cords at birth are more likely to develop chronic rheumatic heart disease in later life. As longer umbilical cords have more spiral arteries and a higher vascular resistance, we hypothesize that the increased pressure load on the heart leads to changes in endothelial biology which makes them more vulnerable to the autoimmune process initiated by infection with β -haemolytic streptococci.

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Conflict of interests:

None

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References

1. Carapetis JR, McDonald M and Wilson NJ. Acute rheumatic fever. *Lancet*. 2005; 366: 155-68.
2. Bryant PA, Robins-Browne R, Carapetis JR and Curtis N. Some of the people, some of the time: susceptibility to acute rheumatic fever. *Circulation*. 2009; 119: 742-53.
3. Morsing E, Liuba P, Fellman V, Marsal K and Brodzki J. Cardiovascular function in children born very preterm after intrauterine growth restriction with severely abnormal umbilical artery blood flow. *European journal of preventive cardiology*. 2013; 23: 23.
4. Mercurio G, Bassareo PP, Flore G, et al. Prematurity and low weight at birth as new conditions predisposing to an increased cardiovascular risk. *Eur J Prev Cardiol*. 2013; 20: 357-67. Epub 2012 Jan 19.
5. Phillips DI. External influences on the fetus and their long-term consequences. *Lupus*. 2006; 15: 794-800.
6. Ligi I, Grandvuillemin I, Andres V, Dignat-George F and Simeoni U. Low birth weight infants and the developmental programming of hypertension: a focus on vascular factors. *Seminars in perinatology*. 2010; 34: 188-92.

7. Eriksson J, Kajantie E, Phillips D, Osmond C, Thornburg K and Barker D. The developmental origins of chronic rheumatic heart disease. *Am J Human Biol.* 2013; 25: 655-8.
8. Koupil I. The Uppsala studies on developmental origins of health and disease. *Journal of Internal Medicine.* 2007; 261: 426-36.
9. Goodman A and Koupil I. Social and biological determinants of reproductive success in Swedish males and females born 1915-1929. *Evol Hum Behav.* 2009; 30: 329-41.
10. Goodman A, Koupil I and Lawson DW. Low fertility increases descendant socioeconomic position but reduces long-term fitness in a modern post-industrial society. *Proceedings Biological sciences / The Royal Society.* 2012; 279: 4342-51.
11. Ludvigsson JF, Andersson E, Ekblom A, et al. External review and validation of the Swedish national inpatient register. *BMC public health.* 2011; 11: 450.
12. White IR and Royston P. Imputing missing covariate values for the Cox model. *Stat Med.* 2009; 28: 1982-98.
13. Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002; 21: 1539-58.
14. Tandon R, Sharma M, Chandrashekar Y, Kotb M, Yacoub MH and Narula J. Revisiting the pathogenesis of rheumatic fever and carditis. *Nature reviews Cardiology.* 2013; 10: 171-7.
15. Dinkla K, Rohde M, Jansen WT, Kaplan EL, Chhatwal GS and Talay SR. Rheumatic fever-associated *Streptococcus pyogenes* isolates aggregate collagen. *The Journal of clinical investigation.* 2003; 111: 1905-12.
16. Dinkla K, Talay SR, Morgelin M, et al. Crucial role of the CB3-region of collagen IV in PARF-induced acute rheumatic fever. *PLoS one.* 2009; 4: e4666.
17. Aird WC. Phenotypic heterogeneity of the endothelium: I. Structure, function, and mechanisms. *Circulation research.* 2007; 100: 158-73.
18. Dewey CF, Jr., Bussolari SR, Gimbrone MA, Jr. and Davies PF. The dynamic response of vascular endothelial cells to fluid shear stress. *Journal of biomechanical engineering.* 1981; 103: 177-85.
19. Aird WC. Endothelial cell heterogeneity. *Critical care medicine.* 2003; 31: S221-30.
20. Butcher JT, Simmons CA and Warnock JN. Mechanobiology of the aortic heart valve. *The Journal of heart valve disease.* 2008; 17: 62-73.
21. Thornburg KL, O'Tierney PF and Louey S. Review: The placenta is a programming agent for cardiovascular disease. *Placenta.* 2010; 31 Suppl: S54-9.
22. Barbera A, Giraud GD, Reller MD, Maylie J, Morton MJ and Thornburg KL. Right ventricular systolic pressure load alters myocyte maturation in fetal sheep. *American journal of physiology Regulatory, integrative and comparative physiology.* 2000; 279: R1157-64.
23. Harman CR and Baschat AA. Comprehensive assessment of fetal wellbeing: which Doppler tests should be performed? *Current opinion in obstetrics & gynecology.* 2003; 15: 147-57.
24. Sader MA and Celermajer DS. Endothelial function, vascular reactivity and gender differences in the cardiovascular system. *Cardiovascular research.* 2002; 53: 597-604.

25. Patterson AJ, Chen M, Xue Q, Xiao D and Zhang L. Chronic prenatal hypoxia induces epigenetic programming of PKC{epsilon} gene repression in rat hearts. *Circulation research*. 2010; 107: 365-73.
26. Jones JA, Stroud RE, Kaplan BS, et al. Differential protein kinase C isoform abundance in ascending aortic aneurysms from patients with bicuspid versus tricuspid aortic valves. *Circulation*. 2007; 116: I144-9.
27. Ramzy D, Tumiati LC, Xu N, et al. Limiting endothelial cell hypoxic injury: the role of isoform specific PKC modulation. *Circulation*. 2006; 114: 353.
28. Roberts WC and Virmani R. Aschoff bodies at necropsy in valvular heart disease. Evidence from an analysis of 543 patients over 14 years of age that rheumatic heart disease, at least anatomically, is a disease of the mitral valve. *Circulation*. 1978; 57: 803-7.