LIFE COURSE EPIDEMIOLOGY

The placental origins of sudden cardiac death

David JP Barker,1,2,3* Gail Larsen,1 Clive Osmond,2 Kent L Thornburg,1 Eero Kajantie4,5 and Johan G Eriksson4,6,7,8,9

1Heart Research Center and Moore Institute, Oregon Health and Science University, Portland, OR, USA, 2MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton General Hospital, Southampton, Hampshire, UK, 3Chair of Fetal Programming, Zoology Department, College of Science, King Saud University, Riyadh, Saudi Arabia, 4Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland, 5Hospital for Children and Adolescents, Helsinki University Central Hospital, Helsinki, Finland, 6Department of General Practice and Primary Health Care, Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland, 7Vasa Central Hospital, Vasa, Finland, 8Folka¨lsan Research Centre, Helsinki, Finland and 9Unit of General Practice, Helsinki University Central Hospital, Helsinki, Finland

*Corresponding author. MRC Lifecourse Epidemiology Unit, (University of Southampton), Southampton General Hospital, Southampton, SO16 6YD, UK. E-mail: djpbarker@gmail.com

Accepted 20 June 2012

Objective

Most sudden cardiac deaths are due to cardiac arrhythmias, and abnormalities in the autonomic nervous system could underlie them. There is growing evidence that coronary heart disease is associated with alterations of fetal development as a result of variations in the processes of placentation that control fetal nutrition. We hypothesized that placental size would be associated with sudden cardiac death.

Methods

We examined sudden cardiac death within the Helsinki Birth Cohort of 13 345 men and women.

Results

One hundred eighty-seven (2.7%) men and 47 (0.7%) women had sudden unexplained cardiac death outside hospital. Sudden death was associated with a thin placenta, the hazard ratio being 1.47 [95% confidence interval (CI) 1.11–1.93, P = 0.006] for each g/cm² decrease in thickness. Sudden death was independently associated with poor educational attainment (P < 0.0001). Both of these associations were independent of socio-economic status in later life.

Conclusion

Sudden death may be initiated by impaired development of the autonomic nervous system in utero as a result of shallow invasion of the spiral arteries in the maternal endometrium and consequent fetal malnutrition.

Keywords

Sudden cardiac death, placenta, educational attainment

Introduction

The worldwide burden of sudden cardiac death is estimated to be 4–5 million cases per year.1 Approximately 80% of people who have sudden cardiac death have underlying coronary heart disease. There is, however, an important distinction between sudden cardiac death, which is thought to be secondary to ventricular arrhythmias, and acute myocardial infarction, which results from occlusion of a coronary artery.2,3 There is growing evidence that coronary heart disease is associated with alterations in prenatal growth.4,5 This has led to the hypothesis that this disease originates in utero as a consequence of fetal malnutrition, which programmes the structure and function of the body in ways that lead to the disease later in life.6 Fetal nutrition depends on the placenta’s ability to transport nutrients from mother to baby. We have recently shown that coronary heart disease.
among men is associated with the shape of the placental surface at birth, as well as with the ratio of placental size to birth size. This leads to the conclusion that the disease is associated with variations in three processes of normal placental development. These may lead to fetal under-nutrition and thereby programme the disease. The processes are (i) implantation and spiral artery invasion, (ii) growth of the chorionic surface and (iii) compensatory expansion of the chorionic surface. Further evidence of a link between placental structure and coronary heart disease comes from the association between reduced placental area at birth and chronic heart failure in later life. A recent report shows that high birthweight is associated with incident atrial fibrillation in women. This suggests that there may be prenatal determinants of other cardiac arrhythmias. We have examined the associations between maternal, placental and fetal size and later sudden cardiac death in the Helsinki Birth Cohort. Sudden cardiac death has been consistently reported to be associated with low socio-economic status, and we therefore examined this in our analysis.

Methods
The Helsinki Birth Cohort includes 6975 men and 6370 women who were born in the city during 1934–44 and attended child welfare clinics. They were born either in the University Central Hospital or in the Maternity Hospital. Details of the birth records have been described. They include the mother’s height and weight in late pregnancy, her age and parity and the date of her last menstrual period, from which we calculated the length of gestation. The weight, head circumference and length of the baby were recorded, and we calculated the ponderal index (birth weight/length³). The records also include the weight of the placenta, together with the maximal so-called ‘diameter’ of the surface and a lesser ‘diameter’ bisecting it at right angles. We refer to these diameters as the length and breadth of the surface. They were measured because, in the past, it was recognized that the placental surface is more oval than circular, and the two diameters were used routinely to describe the shape of the placental surface. The placental measurements were correlated with each other: \( r = 0.58 \) for length and breadth. Assuming an elliptical surface, we estimated the surface area of the placenta as length \( \times \) breadth \( \times \pi/4 \). We used the difference between the length and breadth to determine the degree of ovality of the placental surface. Assuming a constant density, we estimated the thickness of the placenta as weight divided by area.

Based on a classification from Statistics Finland, fathers were grouped into upper and lower middle class and manual workers. The men’s and women’s own occupation, recorded at successive 5-year censuses from 1970 to 2000, and their level of educational attainment were obtained from Statistics Finland. They grouped occupation into four categories—higher official, lower official, self-employed and manual worker. We used the highest category attained. They grouped level of education attained into high (upper secondary and tertiary), middle (lower secondary) and low (primary).

All hospital discharges in Finland are recorded in the national hospital discharge register, and all deaths are recorded in the national mortality register. Using the personal identification number assigned to each Finnish resident, we identified all hospital admissions and deaths from coronary heart disease among the men and women during 1971–2008. In ascertaining sudden death, we used the International Classification of Disease (ICD) codes that define coronary heart disease (410–414 in ICD 9th revision, I21–I25 in ICD 10th revision). We restricted our analysis to deaths, certified as being due to coronary heart disease, which occurred outside hospital among men and women who had never been admitted to hospital with coronary heart disease. We labelled such deaths as ‘sudden cardiac deaths’. Health care is free in Finland, and therefore there are no financial barriers to hospital admission.

Statistical methods
The end point for our survival analysis was sudden death from coronary heart disease. People were censored in the analysis when they migrated from Finland, were hospitalized for coronary heart disease or died. We used a Cox proportional hazards model to calculate the hazard ratios for sudden death for a unit increase in measurements of placental and birth size. The analyses were stratified for year of birth and sex. The measurements were analysed as continuous variables, although they are presented in the tables as groups.

Results
One hundred eighty-seven (2.7%) men and 46 (0.7%) women died suddenly from coronary heart disease outside hospital. Age-adjusted sudden death rates were 137 per 100 000 in men and 48 per 100 000 in women. The mean age at death was 55 years in men and 62 years in women.

Table 1 shows the mean size of the newborn babies and their placentas. Table 2 shows that sudden cardiac death was not associated with birthweight, nor was it associated with head circumference, length, ponderal index or length of gestation in either sex. Sudden death was not associated with placental weight (Table 2) or with the length, breadth and area of the placental surface. It was also not associated with the shape of the placental surface, as described by the difference between the length and breadth. Among women, in a simultaneous analysis with birthweight, sudden death was associated with a large placental area (\( P = 0.05 \)) and low birthweight (\( P = 0.02 \)), so that it was associated with a large
ratio of placental area to birthweight (Table 2). There was no similar finding among men. Table 3 shows that, in men and women combined, hazard ratios for sudden death rose with increasing placental thinness. Although the trend was not statistically significant in women (Table 3), the hazard ratio in those with the thinnest placentas was significantly higher than the hazard ratio in those with the thickest placentas. The association between sudden death and placental thinness tended to be stronger among people who had lower birthweight ($P$ for interaction birthweight $\times$ placental thinness $= 0.1$). In neither sex was birthweight associated with sudden death in a simultaneous regression with placental thinness. The trends with placental thinness were similar among people born after different periods of gestation. Sudden death was not related to maternal age or parity. Its associations with placental thinness were similar in first and later pregnancies.

Socio-economic status

Sudden cardiac death was related to the father’s low social class ($P = 0.003$) and to low social class among the subjects ($P < 0.001$). Table 4 shows that in both men and women, hazard ratios for sudden cardiac death decreased with increasing levels of educational attainment. In a simultaneous regression with these three socio-economic variables, the hazard ratio for sudden death was 1.56 ($1.15–2.11$, $P = 0.004$) per g/cm$^2$ decrease in placental thickness, whereas the effects of low adult social class and poor socio-economic status

### Table 2 Hazard ratios for sudden cardiac death according to birthweight and placental size in men and women

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Men (Cases/subjects)</th>
<th>HR (95% CI)</th>
<th>Women (Cases/subjects)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Birthweight (g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 2500$</td>
<td>7/218</td>
<td>1.5 (0.6–3.6)</td>
<td>4/234</td>
<td>2.8 (0.6–12.4)</td>
</tr>
<tr>
<td>$2500–3000$</td>
<td>19/882</td>
<td>1.0 (0.5–1.8)</td>
<td>8/1201</td>
<td>1.0 (0.3–3.6)</td>
</tr>
<tr>
<td>$3000–3500$</td>
<td>78/2642</td>
<td>1.3 (0.8–2.2)</td>
<td>22/2694</td>
<td>1.1 (0.3–3.6)</td>
</tr>
<tr>
<td>$3500–4000$</td>
<td>64/2385</td>
<td>1.2 (0.7–2.0)</td>
<td>9/1818</td>
<td>0.7 (0.2–2.5)</td>
</tr>
<tr>
<td>$&gt;4000$</td>
<td>19/848</td>
<td>1.0 (baseline)</td>
<td>3/423</td>
<td>1.0 (baseline)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td>1.0</td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Placental weight (g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\leq 550$</td>
<td>45/1544</td>
<td>1.4 (0.9–2.2)</td>
<td>15/1596</td>
<td>1.0 (0.5–2.4)</td>
</tr>
<tr>
<td>$550–650$</td>
<td>69/2309</td>
<td>1.4 (0.9–2.2)</td>
<td>13/2197</td>
<td>0.7 (0.3–1.5)</td>
</tr>
<tr>
<td>$650–750$</td>
<td>45/1858</td>
<td>1.2 (0.7–1.9)</td>
<td>9/1643</td>
<td>0.6 (0.2–1.5)</td>
</tr>
<tr>
<td>$&gt;750$</td>
<td>27/1240</td>
<td>1.0 (baseline)</td>
<td>9/923</td>
<td>1.0 (baseline)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td>0.15</td>
<td></td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Placental area to birthweight ratio (cm$^2$/g)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt;0.07$</td>
<td>58/2402</td>
<td>1.0 (baseline)</td>
<td>11/1946</td>
<td>1.0 (baseline)</td>
</tr>
<tr>
<td>$0.07–0.08$</td>
<td>56/2131</td>
<td>1.1 (0.8–1.6)</td>
<td>13/1807</td>
<td>1.3 (0.6–2.8)</td>
</tr>
<tr>
<td>$0.08–0.09$</td>
<td>44/1421</td>
<td>1.3 (0.9–1.9)</td>
<td>7/1434</td>
<td>0.9 (0.4–2.4)</td>
</tr>
<tr>
<td>$&gt;0.09$</td>
<td>28/971</td>
<td>1.2 (0.8–1.9)</td>
<td>15/1153</td>
<td>2.5 (1.2–5.5)</td>
</tr>
<tr>
<td><strong>P for trend</strong></td>
<td></td>
<td>0.24</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

HR = hazard ratio.
educational attainment remained statistically significant ($P < 0.001$ and $P = 0.007$, respectively). The effect of the father’s low social class was no longer significant ($P = 0.2$). We examined the effect of placental thickness on educational attainment, allowing for adult social class. In men, placental thinness was weakly associated with poor educational attainment (correlation coefficient: $0.03$, $P = 0.04$). There was no similar trend among women.

**Discussion**

We have examined the associations between maternal and placental size and later sudden cardiac death. In both men and women, sudden death was associated with a thin placenta at birth and, independently, with poor educational attainment. These associations were independent of father’s social class and socio-economic status in later life. Sudden cardiac death was not associated with maternal body size or with fetal size at birth or length of gestation, and therefore these cannot be confounding variables in our analyses.

**Placental thinness**

A thin placental surface may be the result of shallow invasion of the spiral arteries in the maternal endometrium. This would reduce the flow of nutrients from mother to fetus. Despite this, babies who had a sudden cardiac death later in life attained a normal birthweight. However, the quality of their development may have been prejudiced, as was seen during the wartime famine in Holland. Babies who were in the first two trimesters of gestation during the famine grew normally, but they had increased rates of cardiovascular disease and type 2 diabetes in later life.

Among women, sudden death was also associated with a placental surface area that was large in relation to the weight of the baby. This suggests that the placenta compensated for a thin surface by expanding the area of the surface. Compensatory placental expansion is well documented in sheep, and manipulation of placental size by changing the pasture of pregnant ewes is standard practice in sheep farming. There is evidence that similar compensatory placental expansion occurs in humans. Compensatory expansion may be beneficial in some circumstances, but if the compensation is inadequate and the fetus continues to be under-nourished, the need to share its nutrients with an enlarged placenta may become a metabolic burden, and the quality of fetal development may be prejudiced. We suggest that the girl fetuses in our study compensated for placental thinness by expanding the placental surface. As a result, their birthweight was lower than would be expected from the surface area of the placenta. Boys invest less in the placenta than girls, which could explain why placental compensation did not occur among them.

**Educational attainment**

Associations between sudden cardiac death and low socio-economic status have been consistently
reported.\textsuperscript{9} We found that sudden cardiac death was strongly associated with low socio-economic status and with low educational attainment. Poor educational attainment may result from poor cognitive ability or from other impairments such as inability to sustain attention. Altered autonomic nervous activity is thought to underlie attention deficit disorder.\textsuperscript{15} We hypothesize that the association between sudden death and poor educational attainment results from impaired prenatal development of the autonomic nervous system.

**Biological processes**

Sudden cardiac arrest is due to abnormal electrical activity in Purkinje cells and/or working cardiomyocytes that leads to ventricular fibrillation, ventricular tachycardia or pulseless electrical activity. It is known that people who die suddenly from cardiac arrest have increased fibrosis in the heart, and it has become increasingly evident that many cases of unexplained sudden cardiac death are related to excessive release of norepinephrine in the myocardium by the sympathetic arm of the autonomic nervous system.\textsuperscript{2,16} We suggest that our findings are consistent with abnormal development of the autonomic nervous system in utero, as a consequence of placental thinness. There is evidence that people who experienced fetal malnutrition and were small at birth have increased sympathoadrenal responses to acute stress.\textsuperscript{17}

**Limitations of the study**

The placental measurements in our study were made during routine obstetric practice 70 years ago. Routine measurements of the placental diameters ceased in Helsinki in the 1970s. We have discussed the simple procedures used with people who worked as midwives at that time. The quality of the measurements was not routinely checked, just as there are no routine checks of other clinical measurements, such as blood pressure. The mean placental weight in our study was more than the median recorded in a recent series of deliveries in Europe.\textsuperscript{18} One explanation for this could be that the cord and membranes were not trimmed before weighing. This would make our estimates of placental thickness less accurate. Measurement errors would tend to diminish associations between placental size and later sudden death. We identified men and women who died outside hospital using the national hospital discharge and mortality registers. The validity of these registers has been established.\textsuperscript{19,20} We used death from coronary heart disease outside hospital, among people who had never been admitted to hospital with coronary heart disease, as a proxy for sudden cardiac death because for subjects who died in a hospital, register data do not allow us to identify those who fulfilled the criteria for sudden cardiac death. In a recent Finnish population study, 84% of sudden cardiac deaths occurred outside hospital.\textsuperscript{21} We do not have data on adult lifestyles and are therefore not able to adjust for this.

**Conclusions**

We suggest that sudden death is initiated by impaired development of the autonomic nervous system in utero as a result of shallow invasion of the spiral arteries in the maternal endometrium and consequent fetal malnutrition. In girls, the effects of this are compounded by compensatory expansion of the placental surface, so that the girls are born with low birthweight in relation to the size of the placental surface.

**Funding**

The study was supported by grants from the Academy of Finland, British Heart Foundation, Finnish Medical Society Duodecim, Finska Läkare-sällskapet, Foundation for Pediatric Research, Jalmari and Rauha Ahokas Foundation, Juho Vainio Foundation, Päivikki and Sakari Sohlberg Foundation, Signe and Ane Gyllenberg Foundation, Yrjö Jahnsson Foundation and the Edwards Endowment.

**Conflicts of interest:** None declared.

---

**KEY MESSAGES**

- Sudden cardiac death was associated with a thin placenta at birth.
- Sudden death was also associated with poor educational attainment.
- Sudden death may be initiated by impaired development of the autonomic nervous system in utero as a result of shallow invasion of the spiral arteries of the maternal endometrium and consequent fetal malnutrition.
- The adverse effects of prenatal malnutrition on the development of the autonomic nervous system may also lead to poor educational attainment.
References