Neighbourhood Deprivation, Individual-Level and Familial-Level Socio-demographic Factors and Risk of Congenital Heart Disease: A Nationwide Study from Sweden.

Li, Xinjun; Sundquist, Jan; Hamano, Tsuyoshi; Zöller, Bengt; Sundquist, Kristina

Published in:
International Journal of Behavioral Medicine

DOI:
10.1007/s12529-015-9488-9

2016

Neighborhood deprivation, individual-level and familial-level sociodemographic factors and risk of congenital heart disease: a nationwide study from Sweden

Xinjun Li[a] MD, PhD; Jan Sundquist[a, b] MD, PhD; Tsuyoshi Hamano[c], PhD; Bengt Zöller[a] MD, PhD; and Kristina Sundquist[a,b] MD, PhD

[a]Center for Primary Health Care Research, Lund University/Region Skåne, Sweden

[b]Stanford Prevention Research Center, Stanford University School of Medicine, California, USA

[c]Centre for Community-based Health Research and Education (COHRE), Organization for the Promotion of Project Research, Shimane University, Izumo, Japan.

Running title: Neighborhood deprivation and congenital heart disease

Words in abstract: 278

Words in manuscript: 2,728

Number of References: 50

Tables 2

Figures 0

Correspondence to: Dr. Xinjun Li, Center for Primary Health Care Research, Lund University/Region Skåne, CRC, building 28, floor 11, Jan Waldenströms gata 35, Skåne University Hospital, 205 02 Malmö Sweden. Phone: +46-40-391381; Fax: +46-40-391370; E-mail: xinjun.li@med.lu.se

Abstract

Objectives: To examine whether there is an association between neighborhood deprivation and incidence of congenital heart disease (CHD), after accounting for family- and individual-level potential confounders.

Methods: All children aged 0 to 11 years and living in Sweden (n = 748,951) were followed between January 1, 2000 and December 31, 2010. Data were analysed by multilevel logistic regression, with family- and individual-level characteristics at the first level and level of neighborhood deprivation at the second level.

Results: During the study period, among a total of 748,951 children, 1499 (0.2%) were hospitalised with CHD. Age-adjusted cumulative hospitalisation rates for CHD increased with increasing level of neighborhood deprivation. In the study population, 1.8 per 1,000 and 2.2 per 1,000 children in the least and most deprived neighborhoods, respectively, were hospitalised with CHD. Incidence of hospitalisation for CHD increased with increasing neighborhood-level deprivation across all family and individual-level sociodemographic categories. The odds ratio (OR) for hospitalisation for CHD for those living in high-deprivation neighborhoods versus those living in low-deprivation neighborhoods was 1.23 (95% confidence interval (CI) =1.04–1.46). In the full model, which took account for age, paternal and maternal individual-level socioeconomic characteristics, comorbidities (e.g. maternal type 2 diabetes, OR = 3.03; maternal hypertension, OR = 2.01), and family history of CHD (OR = 3.27), the odds of CHD were slightly attenuated but did not remain significant in the most deprived neighborhoods (OR=1.20, 95% CI=0.99–1.45, p=0.057).

Conclusions: This study is the largest so far on neighborhood influences on CHD and the results suggests that deprived neighborhoods have higher rates of CHD, which represents important

clinical knowledge. However, the association does not seem to be independent of individual- and family-level characteristics.

Keywords: congenital heart disease, neighborhood-level deprivation, incidence, sociodemographic factors, multilevel modelling

Introduction

Congenital heart disease (CHD) is a major health risk in childhood [1-4], affecting 1% of children. The prognosis varies depending on type and severity of the CHD. Although the specific mechanisms behind CHD are largely unknown, some of the known risk factors include familial history of CHD [5, 6], ethnicity and migration [7], maternal obesity [8], smoking [9, 10], diabetes [11, 12], hypertension [12], rubella infection and influenza during pregnancy [13], phenylketonuria (PKU) [14], and maternal occupational exposure [15]. There is also a growing body of evidence that suggests that individual-level socioeconomic status (SES) is a risk factor for CHD [10, 16-20]. Low SES may influence the risk of CHD in multiple ways. For example, exposure to harmful agents may result from residential, lifestyle or occupational factors, all of which may be related to SES. These individual-level sociodemographic characteristics do not, however, fully explain the disparities of SES in CHD risk that exist between different population groups [19]. Efforts have therefore been made to study whether the socioeconomic environment (e.g., deprivation, social capital) is associated with the risk of CHD. Neighborhood environments have been shown to be an important independent risk factor for many congenital health problems [21-28]. However, no previous studies have investigated whether neighborhood deprivation is associated with CHD after accounting for family- and individual-level factors.

The present study had the following two aims: 1) to determine whether the relationship between neighborhood deprivation and risk of hospitalisation for CHD remains significant after adjusting for family- and individual-level factors; and 2) to examine possible cross-level interactions between individual-level factors and neighborhood-level deprivation to determine whether neighborhood-level deprivation has a differential effect on risk of CHD across subgroups of families and individuals (effect modification).

Methods

Data used in this study were retrieved from a national database that contains information on the entire population of Sweden for a period of 40 years. The dataset we used contains nationwide information on parents and their offspring at the individual and neighborhood levels, including comprehensive demographic and socioeconomic data. The information comes from several Swedish national registers. The registers used in the present study were the Total Population Register, the Multi-Generation Register, the Hospital Discharge Register, and the Out-Patient Register. The Swedish nationwide population and health care registers have exceptionally high completeness and validity [29]. Individuals (children and their parents) were tracked using the personal identification numbers, which are assigned to each resident of Sweden. These identification numbers were replaced with serial numbers to provide anonymity. The follow-up period ran from January 1, 2000 until hospitalisation/out-patient treatment for CHD, death, emigration or the end of the study period on December 31, 2010. In the study period, there were 1213 (0.16%) children who died and 16006 (2.1%) children who emigrated before the age of 11.

Outcome variable: CHD

The outcome variable in this study was a hospital or out-patient diagnosis of CHD (age at diagnosis 0 to 11 years) during the study period. Data on in-patient and out-patient diagnoses of CHD were retrieved from the Hospital Discharge Register and Out-Patient Register, which contain include information on all hospital visits, including diagnoses. We searched these two registers for the International Classification of Diseases (ICD)-10 codes Q20-Q26, denoting CHD as the main diagnosis during the study period. The serial numbers were used to ensure that each individual appeared only once in the dataset, for his or her first diagnosis of CHD during the study period.

Neighborhood-level deprivation

The home addresses of all Swedish individuals have been geocoded to small geographic units with boundaries defined by homogeneous types of buildings. These neighborhood areas, called small area market statistics or SAMS, each contain an average of 1,000 residents and were created by the Swedish Government-owned statistics bureau Statistics Sweden. SAMS were used as proxies for neighborhoods, as they were in previous research [30, 31]. Neighborhood of residence is determined annually using the National Land Survey of Sweden register.

A summary index was calculated to characterise neighborhood-level deprivation. The neighborhood index was based on information about female and male residents aged 20 to 64 because this age group represents those who are among the most socioeconomically active in the population (i.e. a population group that has a stronger impact on the socioeconomic structure in the neighborhood than children, younger women and men, and retirees do). The neighborhood index was based on four items: low education level (<10 years of formal education), low income (income from all sources, including interest and dividends, that is <50% of the median individual income), unemployment (excluding full-time students, those completing military service, and early retirees), and receipt of social welfare. The index of the year 2000 was used to categorise neighborhood deprivation as low (more than one SD below the mean), moderate (within one SD of the mean), and high (more than one SD above the mean) [32].

Individual-level sociodemographic variables

Sex of child: male or female.

Age ranged from 0 to 11 years and was divided into three categories: 0-4, 5-8, and 9-11-years.

Maternal marital status was categorized as (1) married/cohabitating or (2) never married,

widowed, or divorced.

Family income was calculated as annual family income divided by the number of people in the family. The family income measure took into consideration the ages of the family members and used a weighted system whereby small children were given lower weights than adolescents and adults. The sum of all family members' incomes was multiplied by the individual's consumption weight divided by the family members' total consumption weight. The final variable was calculated as empirical quartiles from the distribution.

Maternal and paternal education levels were categorised as completion of compulsory school or less (≤9 years), practical high school or some theoretical high school (10–12 years) and completion of theoretical high school and/or college (>12 years).

Maternal and paternal country of birth was categorised as Sweden, European countries, and others.

Maternal urban/rural status: this variable was included because access to preventive antenatal care may vary according to urban/rural status. Mothers were classified as living in a large city, a middle-sized town, or a small town/rural area. Large cities were those with a population of ≥200,000 (Stockholm, Gothenburg and Malmö); middle-sized towns were towns with a population of ≥ 90,000 but <200,000; small towns were towns with a population of ≥ 27,000 and <90,000; and rural areas were areas with populations smaller than those of small towns. This classification yielded three equally-sized groups.

Mobility: children were classified as length of time lived in neighborhood, i.e., < 5 years (moved) or ≥ 5 years (not moved).

Maternal age at childbirth was classified as <20, 20-24, 25-29, 30-34, 35-39, 40-44, and ≥45 years) and *paternal age at childbirth* was classified as <20, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, and ≥50 years.

Maternal and paternal hospitalisations were defined separately as the first diagnosis of the

diseases in question from the Swedish Hospital Register during the follow-up period of: 1) maternal type 2 diabetes (ICD-10 E11-E14), 2) maternal hypertension (ICD-10 I10-I15), 3) paternal chronic obstructive pulmonary disease (COPD) (ICD-10 J40-J49), and 4) maternal alcoholism and alcohol-related liver disease (ICD-10 F10 and K70).

Maternal smoking history was based on the mother's smoking history during pregnancy and divided into three groups: yes, no, and unknown.

Maternal body mass index (BMI) was calculated as weight(kg)/height^2(m^2), and was defined as BMI < 18.5, 18.5 ≤ BMI ≤ 24.9, 25.0 ≤ BMI ≤ 29.9, BMI ≥ 30, and unknown.

Parental occupation was divided into six categories: 1) farmers, 2) self-employed, 3) professionals, 4) white collar workers, (5) unskilled/skilled workers, and 6) others.

Because CHD is known to cluster in families, children were classified according to whether or not they had a *family history (parents or siblings) of CHD*.

During the study period, there were 141 mothers diagnosed with influenza and no mothers diagnosed with rubella during the pregnancy. There were 7 cases of phenylketonuria (PKU) during the study period. However, there were no associations between these factors and CHD and they were therefore not included as covariates.

Statistical analysis

The rate of hospitalisation for CHD was calculated for the total study population and for each subgroup after assessment of neighborhood of residence for children. Multilevel (hierarchical) logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). The analyses were performed using MLwiN version 2.27. First, a null model was calculated to determine the variance among neighborhoods. Then, to determine the crude odds of CHD by level of neighborhood deprivation, a neighborhood model that included only neighborhood-level deprivation was calculated. Next, a full model that included neighborhood-

level deprivation and sex, age and the family and individual-level variables, added simultaneously to the model, was calculated (Aim 1). Finally, a full model tested for cross-level interactions between the family- and individual-level sociodemographic variables and neighborhood-level deprivation to determine whether the effects of neighborhood-level deprivation on congenital incidence differed across the sociodemographic variables (Aim 2).
Random effects: the between-neighborhood variance was estimated both with and without a random intercept. It was regarded to be significant if it was more than 1.96 times the size of the standard error, in accordance with the precedent set in previous studies [33-35].
For comparison, we also calculated Cox regression models and logistic regression models using the SAS statistical package (version 9.3; SAS Institute, Cary, NC, USA).

Ethical considerations

This study was approved by the Ethics Committee at Lund University.

Results

In the total study population (748,951 children), 20%, 62%, and 18% of children aged 0 to 11 years lived in low-, moderate- and high-deprivation neighborhoods, respectively. During the follow-up period (January 1, 2000 to December 31, 2010), 1,499 children (0.2%) were diagnosed with CHD (Table 1). CHD cumulative rates increased from 1.8 per 1,000 in neighborhoods with low deprivation to 2.0 per 1,000 in neighborhoods with moderate deprivation and 2.2 per 1,000 in neighborhoods with high deprivation. A similar pattern of higher hospitalisation rates with increasing neighborhood deprivation was observed across all family- and individual-level sociodemographic categories and comorbidities.

The OR for CHD for children living in a high- versus low-deprivation neighborhoods in the

crude neighborhood-level model was 1.23 (95% CI=1.04–1.46) (Table 2). Neighborhood-level deprivation did not remain significantly associated with CHD odds after adjustment for age, sex, and the family- and individual-level sociodemographic variables (OR=1.20, 95% CI=0.99–1.45, p=0.057) for high-deprivation versus low-deprivation neighborhoods but for moderate-deprivation versus low-deprivation neighborhoods (OR = 1.17, 95% CI = 1.01–1.35). The OR of CHD was highest in children whose mothers had high BMI, were hospitalised for type 2 diabetes or hypertension, those with advanced maternal age at childbirth, and those with a family history of CHD.

A test for cross-level interactions between the individual-level sociodemographic variables and neighborhood-level deprivation in the context of odds of CHD showed no meaningful cross-level interactions or effect modification.

The between-neighborhood variance (i.e. the random intercept) was more than 1.96 times the size of the standard error in all models, indicating that there were significant differences in CHD incidence between neighborhoods after accounting for neighborhood deprivation and the individual-level variables. Neighborhood deprivation explained 7% of the between-neighborhood variance in the null model (see Table 2). After inclusion of the family- and individual-level variables, the explained variance was 31%.

We performed an additional analysis using logistic regression models and the results were almost identical. In the full model, the OR for CHD was 1.20 (95% CI=1.00–1.45) for children living in the most deprived neighborhoods compared with those living in low deprivation neighborhoods (Supplementary Table 1). We also performed an analysis using Cox regression models. In the full model, the hazard ratio (HR) for CHD was 1.21 (95% CI=1.00–1.46) among children living

in the most deprived neighborhoods compared with those living in low deprivation neighborhoods (Supplementary Table 2).

Discussion

We found that living in a high deprivation neighborhood increased the odds of CHD by 23%. It is noteworthy that we found these results in a country with a comparatively strong system of universal health care and social welfare. Our finding that neighborhood deprivation is associated with higher rates of CHD is consistent with the findings of a small number of previous studies [19]. However, few previous neighbourhood researchers have had access to data enabling them to use CHD as a specific outcome variable and the possibility to adjust for several family-and individual-level covariates. For example, the strongest associations with CHD were found for maternal diabetes type 2 and family history of CHD. Some of the family-and individual-level covariates may have acted as confounders or mediators in the associations between neighbourhood deprivation and CHD.

Level of neighborhood deprivation may influence risk of CHD through a number of general mechanisms, including unfavourable health-related behaviours of women during pregnancy [36-38], neighborhood social disintegration (i.e. criminality, high mobility or unemployment) [33], low social capital [31, 39, 40], and neighborhood stress mediated by factors that can influence immunological and/or hormonal stress reactions [41-43]. Consistent with this hypothesis are the results of a U.S. study, which found that neighborhood socioeconomic disparities were associated with adult CHD [44].

Living in deprived neighborhoods can cause isolation from health-promoting milieus (e.g. safe places to exercise and decent housing) and services. In comparisons of wealthy nations,

associations between neighborhood characteristics and different health outcomes were inconsistent [45]. This implies that neighborhood determinants of health are complex. Such determinants may include access to health care, education, and social services. Access to these services is uneven in the U.S., where the effects of income inequalities on health are more pronounced [46]. For example, low income is associated with high risk of CHD [18, 19].

Neighborhood-level inequities include unequal access to and quality of primary and secondary health care services [47]. In Sweden, medical care is provided to all permanent residents, and primary health care clinics and hospitals are equally distributed and located centrally in all types of neighborhoods [47]. However, the actual number of health care professionals working in primary health care clinics can vary considerably by neighborhood type. This is due to difficulties in recruiting and retaining health care personnel in high-deprivation neighborhoods. The uneven distribution of medical personnel across neighborhoods has also been documented in Canada, another country with universal health care [19].

It is possible that infections are more easily spread in high deprivation neighborhoods. In addition, rubella infection and influenza during pregnancy [13] have been reported to be associated with CHD. In Sweden, however, rubella is very uncommon and no child with rubella has been registered since 1985 [48].

The present study has several limitations. These include the possibility that some selective factors operate in the process of hospitalisation to favour certain children being hospitalised. Affordability of health care is not a selective factor in Sweden, nor is the likelihood of seeking medical advice important because of equal access to primary and hospital care [47]. It is, however, possible that residual confounding exists because socioeconomic status cannot be fully

measured by family income and education level. The Swedish Hospital Discharge Register contains no information about diagnostic procedures, which is a limitation, but any bias this caused would be non-differential. However, with respect to CHD, the overall diagnostic validity of the Hospital Discharge Register is close to 90% [49, 50].

The limitations of the study are countered by its strengths, which include: 1) the ability to analyse data on a large national cohort of children aged 0 to 11 years; 2) the prospective design; 3) the completeness of the data (for example, only 1% of the data on maternal education level and family income were missing); 4) the use of small, well-defined neighborhoods with an average of 1,000 residents; and 5) the ability to adjust for a set of family- and individual-level sociodemographic factors (e.g. age, sex, family income, maternal marital status, parental country of birth, parental education level, urban/rural status, mobility, parental age, maternal and paternal hospitalisation, and family history of CHD). Accounting for family income is particularly important as it is a major confounder that can affect an individual's choice of neighborhood. Another strength is the possibility to generalise our results to other populations (external validity), particularly to populations in industrialised societies.

Conclusions

This prospective nationwide study is the largest so far on neighborhood influences on CHD and the results suggests that deprived neighborhoods have higher rates of CHD, which represents important clinical knowledge. However, the association does not seem to be independent of individual- and family-level characteristics.

Acknowledgements

The authors wish to thank Science Editor Stephen Gilliver for his useful comments on the text.

This work was supported by ALF funding from Region Skåne awarded to Jan Sundquist, Bengt Zöller and Kristina Sundquist, the Swedish Research Council (awarded to Kristina Sundquist), grants to Dr Bengt Zöller from the Swedish Heart-Lung Foundation and The Swedish Research Council. Research reported in this publication was also supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R01HL116381 to Kristina Sundquist. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health

The registers used in the present study are maintained by Statistics Sweden and the National Board of Health and Welfare.

Conflict of interest

Author Xinjun Li declares that he has no conflict of interest.

Author Jan Sundquist declares that he has no conflict of interest.

Author Tsuyoshi Hamano declares that he has no conflict of interest.

Author Bengt Zöller declares that he has no conflict of interest.

Author Kristina Sundquist declares that she has no conflict of interest.

References

1. Blue GM, Kirk EP, Sholler GF, Harvey RP, Winlaw DS. Congenital heart disease: current knowledge about causes and inheritance. *Med J Aust* 2012; **197**: 155-9.
2. Hoffman JI. Congenital heart disease: incidence and inheritance. *Pediatr Clin North Am* 1990; **37**: 25-43.
3. Marino BS, Lipkin PH, Newburger JW et al. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation* 2012; **126**: 1143-72.
4. Rodan L, McCrindle BW, Manlhiot C et al. Stroke recurrence in children with congenital heart disease. *Ann Neurol* 2012; **72**: 103-11.
5. Oyen N, Poulsen G, Wohlfahrt J et al. Recurrence of discordant congenital heart defects in families. *Circ Cardiovasc Genet* 2010; **3**: 122-8.
6. Romano-Zelekha O, Hirsh R, Blieden L, Green M, Shohat T. The risk for congenital heart defects in offspring of individuals with congenital heart defects. *Clin Genet* 2001; **59**: 325-9.
7. Mangones T, Manhas A, Visintainer P, Hunter-Grant C, Brumberg HL. Prevalence of congenital cardiovascular malformations varies by race and ethnicity. *Int J Cardiol* 2010; **143**: 317-22.
8. Mills JL, Troendle J, Conley MR, Carter T, Druschel CM. Maternal obesity and congenital heart defects: a population-based study. *Am J Clin Nutr* 2010; **91**: 1543-9.
9. Alverson CJ, Strickland MJ, Gilboa SM, Correa A. Maternal smoking and congenital heart defects in the Baltimore-Washington Infant Study. *Pediatrics* 2011; **127**: e647-53.
10. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update* 2011; **17**: 589-604.
11. Macintosh MC, Fleming KM, Bailey JA et al. Perinatal mortality and congenital anomalies in babies of women with type 1 or type 2 diabetes in England, Wales, and Northern Ireland: population based study. *Bmj* 2006; **333**: 177.

12. Ul Haq F, Jalil F, Hashmi S et al. Risk factors predisposing to congenital heart defects. *Ann Pediatr Cardiol* 2011; **4**: 117-21.

13. Levy HL, Guldberg P, Guttler F et al. Congenital heart disease in maternal phenylketonuria: report from the Maternal PKU Collaborative Study. *Pediatric research* 2001; **49**: 636-42.

14. Luteijn JM, Brown MJ, Dolk H. Influenza and congenital anomalies: a systematic review and meta-analysis. *Human reproduction* 2014; **29**: 809-23.

15. Thulstrup AM, Bonde JP. Maternal occupational exposure and risk of specific birth defects. *Occupational medicine* 2006; **56**: 532-43.

16. Gilboa SM, Desrosiers TA, Lawson C et al. Association between maternal occupational exposure to organic solvents and congenital heart defects, National Birth Defects Prevention Study, 1997-2002. *Occup Environ Med* 2012; **69**: 628-35.

17. Langlois PH, Brender JD, Suarez L et al. Maternal residential proximity to waste sites and industrial facilities and conotruncal heart defects in offspring. *Paediatr Perinat Epidemiol* 2009; **23**: 321-31.

18. Limbers CA, Emery K, Uzark K. Factors Associated with Perceived Cognitive Problems in Children and Adolescents with Congenital Heart Disease. *J Clin Psychol Med Settings* 2012.

19. Agha MM, Glazier RH, Moineddin R, Moore AM, Guttmann A. Socioeconomic status and prevalence of congenital heart defects: does universal access to health care system eliminate the gap? *Birth Defects Res A Clin Mol Teratol* 2011; **91**: 1011-8.

20. Gorini F, Chiappa E, Gargani L, Picano E. Potential Effects of Environmental Chemical Contamination in Congenital Heart Disease. *Pediatr Cardiol* 2014.

21. Hart D, Atkins R, Matsuba MK. The association of neighborhood poverty with personality change in childhood. *J Pers Soc Psychol* 2008; **94**: 1048-61.

22. Singh GK, Kogan MD, van Dyck PC. A multilevel analysis of state and regional disparities in childhood and adolescent obesity in the United States. *J Community Health* 2008; **33**: 90-102.

23. Navalpotro L, Regidor E, Ortega P et al. Area-based socioeconomic environment, obesity risk behaviours, area facilities and childhood overweight and obesity: socioeconomic environment and childhood overweight. *Prev Med* 2012; **55**: 102-7.

24. Kroll ME, Stiller CA, Murphy MF, Carpenter LM. Childhood leukaemia and socioeconomic status in England and Wales 1976-2005: evidence of higher incidence in relatively affluent communities persists over time. *Br J Cancer* 2011; **105**: 1783-7.

25. Shih M, Dumke K, Goran MI, Simon P. The association between community-level economic hardship and childhood obesity prevalence in Los Angeles. *pEDIATRIC Obesity* 2012.

26. Bammann K, Gwozdz W, Lanfer A et al. Socioeconomic factors and childhood overweight in Europe: results from the multi-centre IDEFICS study. *pEDIATRIC Obesity* 2013; **8**: 1-12.

27. El-Sayed AM, Scarborough P, Galea S. Socioeconomic inequalities in childhood obesity in the United Kingdom: a systematic review of the literature. *Obes Facts* 2012; **5**: 671-92.

28. Grigsby-Toussaint DS, Lipton R, Chavez N et al. Neighborhood socioeconomic change and diabetes risk: findings from the Chicago childhood diabetes registry. *Diabetes Care* 2010; **33**: 1065-8.

29. Rosen M, Hakulinen T. Use of disease registers. In: Ahrens W, Pigeot I, eds. *Handbook of epidemiology*. Berlin: Springer-Verlag 2005:232-51.

30. Cubbin C, Sundquist K, Ahlen H et al. Neighborhood deprivation and cardiovascular disease risk factors: protective and harmful effects. *Scandinavian Journal of Public Health* 2006; **34**: 228-37.

31. Sundquist J, Johansson SE, Yang M, Sundquist K. Low linking social capital as a predictor of coronary heart disease in Sweden: A cohort study of 2.8 million people. *Soc Sci Med* 2006; **62**: 954-63.

32. Winkleby M, Sundquist K, Cubbin C. Inequities in CHD incidence and case fatality by neighborhood deprivation. *American Journal of Preventive Medicine* 2007; **32**: 97-106.

33. Sundquist K, Theobald H, Yang M et al. Neighborhood violent crime and unemployment increase the risk of coronary heart disease: A multilevel study in an urban setting. *Social Science and Medicine* 2006; **62**: 2061-71.

34. Johnell K, Lindstrom M, Melander A et al. Anxiolytic-hypnotic drug use associated with trust, social participation, and the miniaturization of community: a multilevel analysis. *Social Science and Medicine* 2006; **62**: 1205-14.

35. Johnell K, Lindstrom M, Sundquist J, Eriksson C, Merlo J. Individual characteristics, area social participation, and primary non-concordance with medication: a multilevel analysis. *BMC Public Health* 2006; **6**: 52.

36. Lee LJ, Lupo PJ. Maternal Smoking During Pregnancy and the Risk of Congenital Heart Defects in Offspring: A Systematic Review and Metaanalysis. *Pediatr Cardiol* 2012.

37. Lupo PJ, Symanski E, Langlois PH et al. Maternal occupational exposure to polycyclic aromatic hydrocarbons and congenital heart defects among offspring in the national birth defects prevention study. *Birth Defects Res A Clin Mol Teratol* 2012; **94**: 875-81.

38. Franklin WJ, Gandhi M. Congenital heart disease in pregnancy. *Cardiol Clin* 2012; **30**: 383-94.

39. Lofors J, Sundquist K. Low-linking social capital as a predictor of mental disorders: a cohort study of 4.5 million Swedes. *Social Science and Medicine* 2007; **64**: 21-34.

40. Sundquist K, Yang M. Linking social capital and self-rated health: a multilevel analysis of 11,175 men and women in Sweden. *Health Place* 2007; **13**: 324-34.

41. Daniel M, Moore S, Kestens Y. Framing the biosocial pathways underlying associations between place and cardiometabolic disease. *Health Place* 2008; **14**: 117-32.

42. Brosschot JF, Benschop RJ, Godaert GL et al. Influence of life stress on immunological reactivity to mild psychological stress. *Psychosom Med* 1994; **56**: 216-24.

43. McEwen BS, Biron CA, Brunson KW et al. The role of adrenocorticoids as modulators of immune function in health and disease: neural, endocrine and immune interactions. *Brain Res Brain Res Rev* 1997; **23**: 79-133.

44. Diller GP, Inuzuka R, Kempny A et al. Detrimental impact of socioeconomic status on exercise capacity in adults with congenital heart disease. *Int J Cardiol* 2011.

45. Lynch J, Smith GD, Hillemeier M et al. Income inequality, the psychosocial environment, and health: comparisons of wealthy nations. *Lancet* 2001; **358**: 194-200.

46. Lochner K, Pamuk E, Makuc D, Kennedy BP, Kawachi I. State-level income inequality and individual mortality risk: a prospective, multilevel study. *Am J Public Health* 2001; **91**: 385-91.

47. van Doorslaer E, Wagstaff A, Bleichrodt H et al. Income-related inequalities in health: some international comparisons. *Journal of Health Economy* 1997; **16**: 93-112.

48. Bottiger M, Forsgren M. Twenty years' experience of rubella vaccination in Sweden: 10 years of selective vaccination (of 12-year-old girls and of women postpartum) and 13 years of a general two-dose vaccination. *Vaccine* 1997; **15**: 1538-44.

49. Ludvigsson JF, Andersson E, Ekbom A et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; **11**: 450.

50. Centre for Epidemiology. Validity of the diagnoses from the Swedish In-Care Register 1987 and 1995 Swedish. Stockholm: the National Board of Health and Welfare 2000.

Table 1. Distribution of population, number of congenital heart disease (CHD) events, and age-standardized incidence (per 1000) by neighborhood-level deprivation

	Population distribution		CHD events		Neighborhood deprivation		
	No.	(%)	No.	%	Low	Moderate	High
Total population (%)	748951				148871 (20%)	464075 (62%)	136005 (18%)
Total number of CHD events			1499		1.8	2.0	2.2
Gender							
Males	384376	51.3	807	53.8	1.8	2.4	2.4
Females	364575	48.7	692	46.2	1.8	2.0	2.0
Age (years)							
0-4	261589	34.9	805	53.7	2.8	3.2	3.1
5-8	265903	35.5	404	27.0	1.2	1.5	1.9
9-11	221459	29.6	290	19.3	1.2	1.3	1.4
Family income							
Low income	188108	25.1	375	25.0	1.8	1.9	2.1
Middle–low income	187488	25.0	382	25.5	1.7	2.2	2.2
Middle–high income	186308	24.9	330	22.0	1.8	1.7	2.1
High income	187047	25.0	412	27.5	1.8	2.3	2.7
Marital status							
Married/cohabiting	422188	56.4	808	53.9	1.7	2.0	2.2
Never married, Widowed, or divorced	326763	43.6	691	46.1	1.9	2.0	2.2
Maternal country of birth							
Sweden	645287	86.2	1283	85.6	1.8	2.0	2.3
European countries	45240	6.0	90	6.0	2.1	2.2	1.7
Other countries	58424	7.8	126	8.4	1.6	1.8	2.3
Paternal country of birth							
Sweden	644169	86.0	1268	84.6	1.7	2.0	2.2
European countries	49170	6.6	98	6.5	2.0	2.3	1.7
Other countries	55612	7.4	133	8.9	2.4	2.0	2.5
Maternal educational attainment							
≤ 9 years	242702	32.4	564	37.6	2.0	2.1	2.2
10–12 years	278492	37.2	494	33.0	1.6	1.9	2.2
> 12 years	227757	30.4	441	29.4	1.8	2.0	2.4
Paternal educational attainment							
≤ 9 years	246843	33.0	547	36.5	2.0	2.2	2.2
10–12 years	288912	38.6	541	36.1	1.7	1.9	2.3
> 12 years	213196	28.5	411	27.4	1.7	2.0	2.4
Urban/rural status							
Large cities	225046	30.0	481	32.1	1.8	2.2	2.3
Middle-sized towns	299847	40.0	576	38.4	1.8	1.9	2.0
Small towns/rural areas	224058	29.9	442	29.5	1.6	2.0	2.3
Mobility							
Not moved	429024	57.3	733	48.9	1.8	1.8	2.1
Moved	319927	42.7	766	51.1	1.6	2.3	2.3
Maternal age at child birth							
<30	421981	56.3	802	53.5	1.6	2.0	2.0

30-39	308621	41.2	643	42.9	1.8	1.9	2.5
≥ 40	18349	2.4	54	3.6	3.4	2.6	2.8
Paternal age at child birth							
<30	282860	37.8	520	34.7	1.5	1.9	2.1
30-39	386357	51.6	803	53.6	1.8	2.1	2.1
≥ 40	79734	10.6	176	11.7	2.2	1.9	2.6
Maternal occupation							
Farmers	1249	0.2	3	0.2	0.0	1.6	4.7
Self-employed	7260	1.0	8	0.5	1.6	0.8	3.4
Professionals	28769	3.8	66	4.4	2.0	2.6	6.7
White collar workers	177987	23.8	311	20.7	1.7	1.9	2.1
Unskilled/skilled workers	270017	36.1	497	33.2	1.8	1.9	2.1
Others	263669	35.2	614	41.0	1.7	2.2	2.3
Paternal occupation							
Farmers	7168	1.0	13	0.9	2.6	1.8	1.6
Self-employed	22336	3.0	31	2.1	2.2	1.2	1.9
Professionals	52296	7.0	94	6.3	2.1	1.9	1.7
White collar workers	131952	17.6	221	14.7	1.5	1.8	2.9
Unskilled/skilled workers	338277	45.2	654	43.6	1.6	2.0	2.0
Others	196922	26.3	486	32.4	2.0	2.3	2.3
Maternal smoking history							
Yes	138922	18.5	239	15.9	1.4	1.9	1.9
No	545998	72.9	1089	72.6	1.7	1.9	2.3
Unknown	64031	8.5	171	11.4	2.8	3.1	2.2
Maternal BMI							
<18.5	11594	1.5	20	1.3	1.8	1.0	1.4
18.5-24.9	270731	36.1	548	36.6	1.3	1.4	1.6
25.0-29.9	93812	12.5	218	14.5	1.0	1.6	2.1
≥ 30	42805	5.7	133	8.9	2.3	2.8	2.4
Unknown	330009	44.1	580	38.7	2.3	2.5	2.1
Maternal hospitalization for alcoholism and alcohol related diseases							
No	742097	99.1	1489	99.3	1.8	2.0	2.2
Yes	6854	0.9	10	0.7	1.6	1.8	1.2
Maternal hospitalization for type 2 diabetes							
No	745039	99.5	1472	98.2	1.8	2.0	2.1
Yes	3912	0.5	27	1.8	8.7	5.3	9.3
Maternal hospitalization for hypertension							
No	741488	99.0	1470	98.1	1.7	2.0	2.2
Yes	7463	1.0	29	1.9	4.9	4.3	5.7
Paternal hospitalization for chronic lower respiratory disease							
No	743902	99.3	1490	99.4	1.8	2.0	2.2
Yes	5049	0.7	9	0.6	1.3	2.4	1.0
Family history of congenital heart disease							
No	745262	99.5	1471	98.1	1.7	2.0	2.1
Yes	3689	0.5	28	1.9	8.8	4.7	11.0

Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for congenital heart disease; Results of multi-level logistic regression models

	Model 1			Model 2			Model 3			
	OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighborhood-level variable (ref. Low)										
Moderate	1.13	0.98	1.30	1.13	0.98	1.30	1.17	1.01	1.35	0.036
High	1.23	1.04	1.46	1.19	1.00	1.41	1.20	0.99	1.45	0.057
Age				0.88	0.86	0.89	0.87	0.85	0.88	<0.001
Gender to males (ref. Females)				1.11	1.00	1.22	1.11	1.00	1.22	0.057
Family income (ref. High income)										
Middle-high income							0.82	0.71	0.96	0.012
Middle-low income							0.95	0.82	1.10	0.484
Low income							0.83	0.71	0.98	0.021
Marital status (ref. Married/co-habiting)										
Never married, widowed, or divorced							1.01	0.91	1.13	0.842
Maternal country of birth (ref. Born in Sweden)										
European countries							0.96	0.75	1.24	0.764
Others							0.79	0.61	1.03	0.089
Paternal country of birth (ref. Born in Sweden)										
European countries							0.93	0.73	1.18	0.549
Others							1.17	0.91	1.51	0.230
Maternal education attainment (ref. > 12 years)										
≤ 9 years							0.99	0.83	1.17	0.889
10–12 years							0.96	0.83	1.12	0.617
Paternal education attainment (ref. > 12 years)										
≤ 9 years							1.01	0.85	1.18	0.920
10–12 years							0.97	0.83	1.13	0.689
Urban/rural status (ref. Large cities)										
Middle-sized towns							0.91	0.81	1.04	0.162
Small towns/rural areas							0.90	0.79	1.03	0.134
Mobility (ref. Not moved)							1.06	0.95	1.19	0.271
Maternal age at child birth (ref. <30 years)										
30-39							0.98	0.86	1.11	0.764
≥ 40							1.31	0.96	1.78	0.089
Paternal age at child birth (ref. <30 years)										
30-39							1.07	0.94	1.22	0.317
≥ 40							1.06	0.86	1.30	0.549
Maternal socioeconomic status (ref. Professionals)										
Farmers							1.26	0.37	4.25	0.689
Self-employed							0.53	0.25	1.12	0.089
White collar workers							0.76	0.58	1.00	0.057
Blue collar workers							0.78	0.58	1.04	0.089

Others			0.80	0.59	1.07	0.134
Paternal socioeconomic status (ref. Professionals)						
Farmers			1.06	0.57	1.96	0.842
Self-employed			0.88	0.57	1.34	0.549
White collar workers			0.95	0.74	1.22	0.689
Blue collar workers			1.09	0.84	1.40	0.549
Others			1.10	0.85	1.43	0.484
Maternal smoking history (ref. No)						
Yes			0.95	0.82	1.10	0.484
Unknown			1.23	1.03	1.47	0.021
Maternal BMI (ref. 18.5-24.9)						
Unknown			1.40	1.21	1.60	<0.001
<18.5			0.88	0.56	1.38	0.617
25.0-29.9			1.08	0.92	1.27	0.317
≥ 30			1.38	1.14	1.67	0.003
Maternal hospitalization for alcoholism and alcohol related diseases (ref. No)			0.74	0.39	1.38	0.368
Maternal hospitalization for type 2 diabetes (ref. No)			3.03	2.05	4.47	<0.001
Maternal hospitalization for hypertension (ref. No)			2.01	1.38	2.93	<0.001
Paternal hospitalization for chronic lower respiratory disease (ref. No)			0.91	0.47	1.76	0.764
Family history of congenital heart disease (ref. Without family history)			3.27	2.23	4.80	<0.001
Variance (S.E.)	*0.103 (0.054)*	*0.097 (0.054)*		*0.077 (0.053)*	
Explained variance (%)	*7*	*13*		*31*	

Model 1: crude model; model 2: adjusted for age and gender; model 3: full model.

Supplementary Table 1. Odds ratios (OR) and 95% confidence intervals (CI) for congenital heart disease; Results of logistic regression models

	Model 1			Model 2			Model 3			
	OR	95% CI		OR	95% CI		OR	95% CI		P-value
Neighborhood-level variable (ref. Low)										
Moderate	1.14	0.99	1.30	1.14	0.99	1.30	1.18	1.02	1.36	0.026
High	1.24	1.05	1.46	1.19	1.01	1.41	1.20	1.00	1.45	0.056
Age				0.88	0.86	0.89	0.87	0.85	0.88	<.0001
Gender to males (ref. Females)				1.11	1.00	1.22	1.11	1.00	1.23	0.999
Family income (ref. High income)										
Middle-high income							1.01	0.85	1.19	0.950
Middle-low income							0.95	0.82	1.10	0.491
Low income							0.83	0.71	0.98	0.024
Marital status (ref. Married/co-habiting)										
Never married, widowed, or divorced							1.01	0.91	1.13	0.810
Maternal country of birth (ref. Born in Sweden)										
European countries							0.96	0.75	1.24	0.767
Others							0.79	0.61	1.03	0.085
Paternal country of birth (ref. Born in Sweden)										
European countries							0.93	0.73	1.19	0.557
Others							1.17	0.91	1.51	0.220
Maternal education attainment (ref. > 12 years)										
≤ 9 years							0.99	0.83	1.17	0.888
10–12 years							0.96	0.83	1.12	0.635
Paternal education attainment (ref. > 12 years)										
≤ 9 years							1.01	0.85	1.19	0.950
10–12 years							0.97	0.83	1.13	0.671
Urban/rural status (ref. Large cities)										
Middle-sized towns							0.91	0.81	1.03	0.154
Small towns/rural areas							0.90	0.79	1.03	0.131
Mobility (ref. Not moved)							1.06	0.95	1.19	0.296
Maternal age at child birth (ref. <30 years)										
30-39							0.98	0.86	1.11	0.755
≥ 40							1.31	0.96	1.78	0.086
Paternal age at child birth (ref. <30 years)										
30-39							1.07	0.94	1.22	0.310
≥ 40							1.06	0.86	1.30	0.582
Maternal occupation (ref. Professionals)										
Farmers							1.26	0.37	4.25	0.714
Self-employed							0.53	0.25	1.12	0.097
White collar workers							0.76	0.58	1.01	0.055
Blue collar workers							0.78	0.59	1.04	0.094

Others	0.80	0.59	1.06	0.123
Paternal occupation (ref. Professionals)				
Farmers	1.11	0.61	2.01	0.729
Self-employed	0.93	0.63	1.36	0.688
White collar workers	1.06	0.82	1.35	0.673
Blue collar workers	1.14	0.96	1.36	0.122
Others	1.16	0.96	1.40	0.129
Maternal smoking history (ref. No)				
Yes	0.95	0.82	1.10	0.481
Unknown	1.23	1.03	1.47	0.024
Maternal BMI (ref. 18.5-24.9)				
Unknown	1.40	1.22	1.60	<.0001
<18.5	0.88	0.56	1.38	0.585
25.0-29.9	1.08	0.92	1.27	0.325
≥ 30	1.38	1.14	1.67	0.001
Maternal hospitalization for alcoholism and alcohol related diseases (ref. No)	0.74	0.40	1.38	0.346
Maternal hospitalization of type 2 diabetes (ref. No)	3.03	2.05	4.47	<.0001
Maternal hospitalization of hypertension (ref. No)	2.01	1.38	2.93	0.000
Paternal hospitalization of chronic lower respiratory disease (ref. No)	0.91	0.47	1.76	0.785
Family history of congenital heart disease (ref. Without family history)	3.37	2.31	4.91	<.0001

Model 1: crude model; model 2: adjusted for age and gender; model 3: full model.

Supplementary Table 2. Hazards ratios (OR) and 95% confidence intervals (CI) for congenital heart disease; Results of cox regression models

	Model 1			Model 2			Model 3			
	HR	95% CI		HR	95% CI		HR	95% CI		P-value
Neighborhood-level variable (ref. Low)										
Moderate	1.14	1.00	1.31	1.14	0.99	1.31	1.18	1.03	1.37	0.021
High	1.25	1.06	1.47	1.20	1.02	1.42	1.21	1.00	1.46	0.048
Age				0.88	0.86	0.89	0.87	0.85	0.88	<.0001
Gender to males (ref. Females)				1.10	1.00	1.22	1.11	1.00	1.22	0.055
Family income (ref. High income)										
Middle-high income							0.82	0.70	0.95	0.008
Middle-low income							0.95	0.82	1.10	0.470
Low income							0.83	0.71	0.98	0.025
Marital status (ref. Married/co-habiting)										
Never married, widowed, or divorced							1.01	0.90	1.12	0.907
Maternal country of birth (ref. Born in Sweden)										
European countries							0.95	0.74	1.23	0.716
Others							0.78	0.60	1.02	0.068
Paternal country of birth (ref. Born in Sweden)										
European countries							0.92	0.72	1.18	0.514
Others							1.17	0.90	1.50	0.238
Maternal education attainment (ref. > 12 years)										
≤ 9 years							0.99	0.83	1.17	0.883
10–12 years							0.96	0.82	1.11	0.563
Paternal education attainment (ref. > 12 years)										
≤ 9 years							1.01	0.86	1.19	0.918
10–12 years							0.96	0.83	1.12	0.633
Urban/rural status (ref. Large cities)										
Middle-sized towns							0.91	0.80	1.03	0.134
Small towns/rural areas							0.91	0.79	1.03	0.145
Mobility (ref. Not moved)							1.07	0.96	1.20	0.220
Maternal age at child birth (ref. <30 years)										
30-39							0.98	0.86	1.11	0.715
≥ 40							1.30	0.96	1.77	0.091
Paternal age at child birth (ref. <30 years)										
30-39							1.08	0.95	1.22	0.265
≥ 40							1.07	0.87	1.32	0.504
Maternal occupation (ref. Professionals)										
Farmers							1.25	0.37	4.22	0.719
Self-employed							0.54	0.26	1.13	0.100
White collar workers							0.76	0.58	1.00	0.053
Blue collar workers							0.78	0.59	1.04	0.096
Others							0.80	0.59	1.06	0.123
Paternal occupation (ref. Professionals)										

Farmers	1.11	0.62	2.01	0.725
Self-employed	0.90	0.61	1.32	0.590
White collar workers	1.06	0.83	1.36	0.648
Blue collar workers	1.15	0.97	1.36	0.115
Others	1.17	0.97	1.42	0.106
Maternal smoking history (ref. Yes)				
Yes	0.95	0.82	1.10	0.492
Unknown	1.24	1.04	1.49	0.019
Maternal BMI (ref. 18.5-24.9)				
Unknown	1.40	1.22	1.61	<.0001
<18.5	0.89	0.57	1.38	0.593
25.0-29.9	1.08	0.92	1.26	0.374
≥ 30	1.38	1.14	1.67	0.001
Maternal hospitalization for alcoholism and alcohol related diseases (ref. No)	0.74	0.40	1.38	0.342
Maternal hospitalization of type 2 diabetes (ref. No)	3.02	2.05	4.44	<.0001
Maternal hospitalization of hypertension (ref. No)	2.01	1.38	2.92	<0.001
Paternal hospitalization of chronic lower respiratory disease (ref. No)	0.91	0.47	1.76	0.785
Family history of congenital heart disease (ref. Without family history)	3.36	2.31	4.88	<.0001

Model 1: crude model; model 2: adjusted for age and gender; model 3: full model.