Congenital heart disease (CHD) accounts for nearly one-third of all major congenital anomalies. CHD birth prevalence worldwide and over time is suggested to vary; however, a complete overview is missing. This systematic review included 114 papers, comprising a total study population of 24,091,867 live births with CHD identified in 164,396 individuals. Birth prevalence of total CHD and the 8 most common subtypes were pooled in 5-year time periods since 1930 and in continent and income groups since 1970 using the inverse variance method. Reported total CHD birth prevalence increased substantially over time, from 0.6 per 1,000 live births (95% confidence interval [CI]: 0.4 to 0.8) in 1930 to 1934 to 9.1 per 1,000 live births (95% CI: 9.0 to 9.2) after 1995. Over the last 15 years, stabilization occurred, corresponding to 1.35 million newborns with CHD every year. Significant geographical differences were found. Asia reported the highest CHD birth prevalence, with 9.3 per 1,000 live births (95% CI: 8.9 to 9.7), with relatively more pulmonary outflow obstructions and fewer left ventricular outflow tract obstructions. Reported total CHD birth prevalence in Europe was significantly higher than in North America (8.2 per 1,000 live births [95% CI: 8.1 to 8.3] vs. 6.9 per 1,000 live births [95% CI: 6.7 to 7.1]; p < 0.001). Access to health care is still limited in many parts of the world, as are diagnostic facilities, probably accounting for differences in reported birth prevalence between high- and low-income countries. Observed differences may also be of genetic, environmental, socioeconomic, or ethnic origin, and there needs to be further investigation to tailor the management of this global health problem. (J Am Coll Cardiol 2011;58:2241–7) © 2011 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AoS = aortic stenosis
ASD = atrial septal defect
CHD = congenital heart disease
CI = confidence interval
Coarc = coarctation of the aorta
GUCH = grown-up congenital heart disease
PDA = patent ductus arteriosus
PS = pulmonary stenosis
TGA = transposition of the great arteries
TOF = tetralogy of Fallot
VSD = ventricular septal defect

The search was limited to original research papers with English abstracts. No time restriction for publication dates was used. Reports of large governmental birth registries were searched online.

All titles and abstracts were screened for study population (live births, children), type of CHD, and birth prevalence. Studies were eligible if they reported the birth prevalence of total CHD or 1 of the 8 most common CHD subtypes: ventricular septal defect (VSD), atrial septal defect (ASD), pulmonary stenosis (PS), patent ductus arteriosus (PDA), tetralogy of Fallot (TOF), coarctation (Coarc), transposition of the great arteries (TGA), and aortic stenosis (AoS). CHD was defined according to the definition of Mitchell et al. (6); namely, “a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance.” This definition excludes PDA in premature infants, Marfan syndrome, bicuspid aortic valve, mitral valve prolapse, cardiomyopathies, and congenital arrhythmias. Papers studying only specific groups (e.g., only Down syndrome), rheumatic heart disease, or case studies of rare defects were excluded. Papers focusing on etiology, (pre-natal) diagnosis, treatment, prognosis, or animal research were also excluded.

After exclusion on the basis of the title and abstract, full papers were carefully read and reconsidered according to all abovementioned inclusion and exclusion criteria. Studies focusing on CHD prevalence in schoolchildren age >5 years or including only severe forms of CHD were excluded. When a study was eligible for inclusion, we verified the denominator and numerator and recalculated the estimated birth prevalence to check accuracy. Studies with incorrect or missing denominators or numerator were excluded. Three authors performed the search independently using these inclusion and exclusion criteria. In case of disagreement, an agreement was negotiated. References of selected papers were crosschecked with the same inclusion and exclusion criteria.

Data extraction. Selected papers were reviewed and study characteristics were tabulated in a MS Excel for Windows (Microsoft Corporation, Redmond, Washington) and Review Manager version 5.0 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The following study characteristics were registered: time period during which the study was performed, country, study design (retrospective or prospective), age of patients, diagnostic method, number of live births, number of patients with CHD, and birth prevalence of total CHD and 8 CHD subtypes. Studies were grouped according to 5-year time periods since 1930 to demonstrate time trends. Time period is taken as the period in which the study was performed. Before 1970, many differences in availability of diagnostic and registration facilities between the continents existed, so we used only those studies performed after 1970 to compare continents and income groups. World Bank Income groups based on gross national income per capita in 2008 were defined as: low income ($<975), lower-middle-income ($976 to $3,855), upper-middle-income ($3,856 to 11,905), and high income ($≥11,906) (7).

Statistical analysis. Statistical analyses were done in Review manager 5.0, MS Excel, and SPPS version 15.0 (SPSS, Chicago, Illinois). Birth prevalence of total CHD and the 8 most common subtypes were pooled using the inverse variance method. Pooled group estimates were compared with a chi-square test. Time trends were plotted by using the Savitzky–Golay smoothing technique. Heterogeneity on basis of study design (retrospective vs. prospective), study size, continents, income groups and time periods was explored by using the Q and the I² statistics and by means of funnel plots.

Results

Search results. The systematic literature search yielded 1,136 potential eligible studies. After exclusion, cross-referencing, and reaching agreement on 3 studies, 114 studies were included in this systematic literature review and meta-analysis (Fig. 1, Online Table 1). This resulted in a total study population of 24,091,867 live births with CHD identified in 164,396 individuals. There were 12 reports of prospective birth defect registries. Seventy-six studies used echocardiography as the main diagnostic tool; the rest used combinations of diagnostic tools, such as death certificates, autopsy and surgical reports, physical examination, x-rays, and catheterization.

Total CHD birth prevalence. Over time, the reported total CHD birth prevalence increased substantially (Fig. 2), from 0.6 per 1,000 live births (95% confidence interval [CI]: 0.4 to 0.8) in 1930 to 1934 to 9.1 per 1,000 live births (95% CI: 9.0 to 9.2) after 1995. The increase over time was S-shaped, with a first steep increase from 1930 to 1960, followed by stabilization around 5.3 per 1,000 live births from 1961 to 1975, a second steep increase from the late 1970s until 1995, and eventually stabilization around 9.1 per 1,000 live births in the last 15 years.

Significant geographical differences were found (Fig. 3A). The highest reported total CHD birth prevalence was found in Asia (9.3 per 1,000 live births [95% CI: 8.9 to 9.7]) and the lowest in Africa (1.9 per 1,000 live births [95% CI: 1.1 to 3.5]). Reported total CHD birth prevalence in Asia was significantly higher compared with all other continents (all, p < 0.001). Europe had the second highest reported total CHD birth prevalence (8.2 per 1,000 live births [95% CI: 8.1 to 8.3]).
Significant differences between World Bank income groups were found (Fig. 3B), with the highest reported total CHD birth prevalence in high-income countries (8.0 per 1,000 live births [95% CI: 7.9 to 8.1]; all, p < 0.001). Reported total CHD birth prevalence in upper-middle-income countries was 7.3 per 1,000 live births (95% CI: 6.9 to 7.7) and 6.9 per 1,000 live births (95% CI: 6.1 to 7.7) in lower-middle-income countries (p = 0.013). No data from low-income countries were available.

Birth prevalence of the 8 most common subtypes of CHD. Reported birth prevalence of the 8 most common CHD subtypes since 1945 is shown in Figure 4. Distribution of the 8 most common CHD subtypes worldwide is shown with percentages in Figure 5. Worldwide reported birth prevalence of the CHD subtypes (per 1,000 live births) was: VSD, 2.62 (95% CI: 2.59 to 2.65); ASD, 1.64 (95% CI: 1.61 to 1.67); PDA, 0.87 (95% CI: 0.83 to 0.91); PS, 0.50 (95% CI: 0.48 to 0.52); TOF, 0.34 (95% CI: 0.31 to 0.37); Coarc, 0.34 (95% CI: 0.32 to 0.36); TGA, 0.31 (95% CI: 0.28 to 0.34); and AoS, 0.22 (95% CI: 0.20 to 0.24).

Significant geographical differences in reported birth prevalence of the 8 most common CHD subtypes were detected (Fig. 5). Asia reported relatively more pulmonary outflow obstructions (PS and TOF) and fewer left ventricular outflow tract obstructions (Coarc and AoS). Furthermore, Asia reported a lower TGA birth prevalence compared with Europe, North America, South America, and Oceania (p < 0.001).

Figure 1 Flow Chart of Study Selection
Flow chart representing the selection of studies during the systematic literature search. Initial search yielded 1,136 potential eligible studies. After reading titles and abstracts, 958 papers were excluded on the basis of exclusion criteria named in the search strategy paragraph of the Methods section. Another 70 papers were excluded after evaluation of full text and recalculating denominators and nominators. Cross-referencing led to inclusion of 6 additional papers, after which 114 papers were included in this systematic review.

Figure 2 Total CHD Birth Prevalence Over Time
Time course of reported total congenital heart disease (CHD) birth prevalence from 1930 until 2010. The blue line shows the time trend, and the squares represent the calculated birth prevalence values for each time period.
Heterogeneity, subgroup analyses, and publication bias. Significant heterogeneity was observed within pooled estimates for all time periods, continents and income groups (all $I^2$ statistic $= 100%$; $Q$ statistic, $p < 0.001$). Birth prevalence estimates did not differ significantly between prospectively and retrospectively designed studies or between large and small studies. Funnel plots were symmetrical.

Discussion

This meta-analysis is the first to systematically compile the available published evidence on worldwide CHD birth prevalence over the past century. Changes over time in CHD birth prevalence. Over time, the reported total CHD birth prevalence increased substan-
tially, from <1 per 1,000 live births in 1930 to 9 per 1,000 live births in recent years. With a worldwide annual birth rate around 150 million births (8), this corresponds to 1.35 million live births with CHD every year, representing a major public health issue.

The increase in reported total CHD birth prevalence over time may be caused by changes in diagnostic methods and screening modalities rather than representing a true increase. Over the past century, knowledge about diagnostics and treatment of CHD increased considerably. Survival increased dramatically due to improvements in the field of cardiothoracic surgery and anesthesia. Specialized pediatric cardiologists were trained, and large prospective birth defect registries became available. Before the era of echocardiography, detection of CHD was dependent on autopsy reports, death certificates, physical examination, x-rays, catheterization, and surgical reports. Therefore, only severely affected subjects could be detected. In the 1970s, echocardiography was widely introduced into clinical practice, making it possible to also diagnose asymptomatic patients as well as patients with mild lesions (9). This development probably explains the increased birth prevalence of total CHD in the 1970s, as well as the increase in specific groups, such as patients with VSD, ASD, and PDA. Furthermore, echocardiography currently is often used as a screening tool before (noncardiac) surgery or full assessment in case of noncardiac disease, causing an increase in diagnoses of minor lesions such as a small VSD or ASD. Our results confirm findings from the Metropolitan Atlanta Congenital Defects Program that routine use of echocardiography has increased diagnosis of minor defects (10). The relative stability of the estimation of birth prevalence of complex CHD subtypes also argues for a merely methodological increase.

Nonetheless, there are arguments that not only the reported but also the true CHD birth prevalence changed over time. Survival of premature infants has improved over the last century, attributing to an increase in total CHD and especially VSD birth prevalence (4). Because increasing numbers of women in developed countries are delaying childbearing to an older age, maternal age has increased in the last decades, consequently causing a higher birth prevalence of congenital abnormalities (11,12). In addition, the patient population with GUCH is steadily increasing and their offspring is at increased risk of having a congenital abnormality (13). Furthermore, one might hypothesize that changes in environmental exposures—for example, due to industrialization and urbanization—over the past century have had effects on CHD birth prevalence. However, only maternal pre-gestational diabetes mellitus, phenylketonuria, febrile illness, infections, various therapeutic drug expo-

![Birth Prevalence of CHD Subtypes Over Time](image-url)
sures, vitamin A use, marijuana use, and exposure to organic solvents have been proven to be associated with increased risk of CHD (14). Exposure to ionizing radiation in occupational settings or in clinical practice did not show any associations with CHD birth prevalence (14). Data about alcohol consumption, hard drugs, or cigarette smoking during pregnancy are insufficient to determine risk for CHD. The impact of increased use of fetal echocardiography and pregnancy termination on reduction of CHD birth prevalence is expected in the next time periods (15). Furthermore, in the upcoming decades we will probably see the effect of improving figures on infant survival and socioeconomic circumstances in developing countries on CHD birth prevalence.

Geographical and income group differences in CHD birth prevalence. Important geographical differences were found. Asia reported the highest total CHD birth prevalence (9.3 per 1,000 live births). This finding could in part be attributed to high consanguinity rates in some study populations (e.g., in Iran and India) (16,17). CHD birth prevalence among children with consanguineous parents was found to be considerably higher than in nonconsanguineous parents, suggesting an important genetic influence (16). Very interesting is the relatively high birth prevalence of pulmonary outflow tract obstructions (PS and TOF) and low birth prevalence of left ventricular outflow tract obstructions (Coarc and AoS) in Asia. These findings confirm the results of Jacobs et al. (18), who found that white children seem to have more left ventricular obstructive lesions, whereas Chinese children have more right ventricular outflow tract lesions. A possible explanation could be found in genetic origin.

Interestingly, Europe had the second highest reported total CHD birth prevalence. The difference between Europe and North America (8.2 vs. 6.9 per 1,000 live births; p < 0.001) was unexpected because the study populations and design of the studies in these 2 continents are quite comparable. This difference might be attributed to ethnic, socioeconomic, and environmental differences. North America has a relatively larger population of African-American inhabitants and, as previously described, CHD is less common in this population (19). Part of the difference might also be explained by differences in healthcare and referral systems. In the United States, as was noted in the Baltimore-Washington Infant Study (20), referral of infants with developmental abnormalities, such as Down syndrome and other trisomies, for cardiac evaluation can be inhibited, whereas these societal factors probably are of less importance in most European countries. Moreover, the fact that we found important differences in CHD birth prevalence according to income status also argues in favor of the fact that lack of resources, medical insurance, screening programs, and referral systems probably lead to an underestimation of the true birth prevalence.

Heterogeneity in this meta-analysis. Obviously, reported birth CHD prevalence reflects the true CHD birth prevalence but also depends on the study design of the original papers, study population selection, and diagnostic tools used. CHD prevalence highly depends on age and gestational age. For example, PDA in preterm babies is a
functional abnormality, whereas it is an abnormality in term infants (21). Furthermore, CHD prevalence highly depends on the sensitivity and specificity of the detection method. Differences in study population selection and inclusion and exclusion criteria of included studies attributed to heterogeneity in this meta-analysis. Tests for heterogeneity showed high heterogeneity in continents, income groups, and time periods, but this finding can be explained by the fact that, due to the very large sample sizes, point estimates were very precise and SEs very small, and therefore heterogeneity was expected and inevitable. We did not find bias caused by the design (prospective or retrospective nature) or size of included studies.

Study limitations. Even though we investigated all available reports of total CHD and CHD subtype birth prevalence worldwide, checked for bias caused by study design, and adjusted comparisons to the era of echocardiography, some residual bias may be present in our estimates (e.g., caused by differences in quality of the papers). It remains difficult, as stated by others, to determine whether detected differences in CHD birth prevalence are real or merely methodological (22). Another inevitable limitation of this meta-analysis is that it does not really cover the entire world population. Data from developing countries were scarce, and studies often do not include indigenous inhabitants and tribes. Population-wide prospective birth defect registries are necessary to determine the true birth prevalence, including economically developing parts of the world.

Conclusions

Reported total CHD birth prevalence increased substantially over the last century, reaching a stable estimate of 9 per 1,000 live births in the last 15 years. This corresponds to 1.35 million newborns with CHD every year, representing a major global health burden. Significant geographical differences were found. It remains uncertain whether detected differences in CHD birth prevalence represent true or merely methodological differences. In the future, the etiology of CHD needs to be further clarified and population-wide prospective birth defect registries covering the entire world population are needed to determine the exact birth prevalence.

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APPENDIX

For a supplementary table, please see the online version of this paper.