Objective  To identify the proportion of major structural noncardiac anomalies identified with congenital heart defects (CHDs).

Study design  Records of infants with CHDs in the Metropolitan Atlanta Congenital Defects Program who were born during the period 1968 through 2005 were classified as having isolated, syndromic, multiple CHD (ie, having an unrecognized pattern of multiple congenital anomalies or a recognized pattern of multiple congenital anomalies of unknown etiology), or laterality defects. Frequencies of associated noncardiac anomalies were obtained.

Results  We identified 7984 live-born and stillborn infants and fetuses with CHDs. Among them, 5695 (71.3%) had isolated, 1080 (13.5%) had multiple, 1048 (13.1%) had syndromic, and 161 (2.0%) had laterality defects. The percentage of multiple congenital anomalies was highest for case with atrial septal defects (18.5%), cardiac looping defects (17.2%), and conotruncal defects (16.0%), and cases with atrioventricular septal defects represented the highest percentages of those with syndromic CHDs (66.7%).

Conclusions  Including those with syndromes and laterality defects, 28.7% of case infants with CHDs had associated major noncardiac malformations. Thus, infants with CHDs warrant careful examination for the presence of noncardiac anomalies. (J Pediatr 2011; 158: 471-478).

Congenital heart defects (CHDs), which occur among approximately 3 to 9 of every 1000 live births, are the most common type of birth defects1-3 and contribute significantly to infant morbidity and mortality.4 Although in most instances the heart defects are isolated, an important proportion of patients with CHDs have additional noncardiac major malformations.1 Some of these case patients have chromosomal or single-gene determined syndromes and others have not previously defined patterns of multiple congenital anomalies (MCAs).

In previously selected reports, proportions of additional structural noncardiac anomalies among children with CHDs range from 14.5% to 66.0%,5,6 depending mainly on the type of ascertainment (Table I). The highest proportion of additional anomalies (45.9% to 66.0% in selected reports) has been identified in studies based on autopsy reports,5,7 followed by clinical studies (14.5% to 30.1%)8,9 and epidemiological studies (16.9% to 25.8%).10-12 Also, the reported prevalence of the different types of cooccurring anomalies varies significantly. For example, Hanna et al1 identified 5.2% of case patients with chromosomal and single-gene syndromes and 18.3% with undefined patterns of MCAs, and Ferencz et al13 reported 17.3% of case patients with chromosomal and single-gene syndromes and 5.9% with MCAs. Regarding the type of additional noncardiac defects, Güçer et al7 found that the most frequently occurring noncardiac defects were craniofacial (19.7%), genitourinary (15.1%), and musculoskeletal (13.4%); however, Calzolari et al12 reported that the most frequently found noncardiac defects were musculoskeletal (25.3%), genitourinary (22.9%), and gastrointestinal (11.5%).

The wide variation in the proportion and type of MCAs reported in studies of CHDs has been due mainly to differences in the types of case ascertainment and defect classifications. Clarification of some of these differences could be obtained from a population-based study using data from an active surveillance system in which clinicians classify cardiac and noncardiac defects in a standardized manner. Findings from such a study might help to better guide studies of the etiologies of CHDs, which remain largely unknown; to understand the pathogenesis of CHDs; to study health outcomes among people with CHDs; and to counsel affected families.
Our study identified the proportion of infants with additional noncardiac anomalies and characterized the types and distributions of these entities among case infants with CHDs in a large, population-based birth defects surveillance system.

### Methods

We identified all live-born and stillborn infants and elective terminations of pregnancy (TOPs) with diagnosed CHDs delivered during the period 1968 through 2005 that were ascertained by the Metropolitan Atlanta Congenital Defects Program (MACDP). MACDP was granted authority to conduct birth defect surveillance in the five central counties of metropolitan Atlanta in collaboration with and on behalf of the Georgia Division of Public Health by the Georgia Department of Human Resources and has CDC’s Institutional Review Board approval. MACDP is an ongoing, population-based birth defects surveillance system established in 1967 to actively monitor birth defects among the offspring of women living in any of the five central counties of metropolitan Atlanta, Georgia, at the time of delivery. The program routinely collects data on clinical and demographic characteristics of live-born and stillborn infants and pregnancies terminated at or after 20 weeks of gestation that present with structural birth defects. Major structural defects, chromosomal abnormalities, and clinical syndromes diagnosed within 6 years of delivery are included in MACDP. The defects are coded using a modified 6-digit code from the International Classification of Diseases, Ninth Revision, Clinical Modification and the British Paediatric Association Classification of Diseases developed for MACDP. Further details about this system have been published elsewhere.14

All MACDP records of infants with cardiac defect 6-digit codes were reviewed and classified by experts in pediatric cardiology, according to a standard clinical nomenclature adapted from the Society of Thoracic Surgeons (STS) and a morphogenetic three-level classification system previously described.15 The grouping of CHDs into higher-order aggregation levels aids in monitoring and research; in the current study, nine major broad categories were used—cardiac looping defects, conotruncal defects, atriocentric right ventricle defects (AVSDs), left ventricular outflow tract obstructive defects (LVOTOs), right ventricular outflow tract obstructive defects (RVOTOs), atrial septal defects (ASDs), ventricular septal defects (VSDs), cell growth defects, and Ebstein anomaly.16 Specific cardiac defects included in the broad STS categories are presented in the Appendix (available at www.jpeds.com). Newborn conditions and those of prematurity were not considered structural abnormalities; patent ductus arteriosus was only counted as a CHD if occurring in nonpremature infants, persisting beyond 6 weeks of life, and not maintained patent for another cardiac condition. Inlet-type VSDs were included in the AVSD category and malaligned or conoventricular-type VSDs in the conotruncal category. Using STS nomenclature, most case infants had only one CHD. However, if a case infant had more than one independent lesion, each CHD was counted separately.15

Clinical information was reviewed by a clinical geneticist (J.F.), who classified cases as having isolated, MCA, or syndromic CHDs based on etiology and the presence and pattern of major structural noncardiac anomalies. Noncardiac anomalies were defined as “major” if they had surgical, medical, or serious cosmetic importance.17 Cases were considered “isolated” when no noncardiac major malformations were present; cases were considered MCAs when at least one major additional noncardiac malformation was found. Also, cases with known associations (eg, the vertebral, anal, cardiac, tracheo-esophageal, renal, and limb association) were classified as having MCAs. Those with
chromosomal anomalies, single-gene disorders, and terato-
genic syndromes were counted among syndromes. Cases of laterality defects with CHDs (eg, heterotaxy syndromes) were analyzed separately because they comprise a specific and broad spectrum of cardiac and non-cardiac abnormalities. We selected 46 specific noncardiac defects for individual analysis. These defects were selected because they are reliably ascertained with the presence of a CHD and previously have been suggested as commonly occurring in association with CHDs.

**Statistical Analysis**

We estimated the proportion of each type of CHD by demographic characteristics, including birth year (1968 to 1980, 1981 to 1992, and 1993 to 2005), maternal race (white, black or African American, and other), sex (male and female), and maternal age (younger than 35 years of age and 35 years of age or older), and clinical covariates such as plurality (singleton and twins or higher), birth outcome (live birth, stillbirth, and TOP), death of live-born infant (died and did not die), autopsy status (yes and no), birth weight (<2500 g and ≥2500 g), preterm birth (<37 weeks’ and ≥37 weeks’ gestation), and prior pregnancy loss among multigravid women (no prior loss and at least one prior pregnancy loss).

We examined various birth cohorts (1968 to 1980, 1981 to 1992, and 1993 to 2005) because over time there were differences in diagnostic techniques used to identify defects, thereby potentially affecting ascertainment. The racial and ethnic categories were white, black or African American, and other, which comprised Hispanic, American Indian or Alaska Native, Asian, and Native Hawaiian or other Pacific Islander groups. The race or ethnicity category was self-identified by the mother in the medical record.

We obtained frequencies of individual associated noncardiac anomalies for CHDs as a group and for each of the cardiac defect categories among case infants with MCAs. We did not carry out this analysis among case infants with syndromes because the syndromes identified were highly heterogeneous and the associated anomalies varied according to the specific condition. We did not examine patterns of malformations for the same child with MCAs, because it would have been too complex and varied to try to address.

For statistical analysis, we used a one-way χ² test, which is basically an independence test with the null hypothesis that the distribution of case infants across values of the single category does not depend on the level of the selected demographic and clinical factors (such as time period, maternal race, maternal age, infant sex, plurality, birth outcome, and expiration after birth). A probability value of P < .05 was regarded as significant. We used SAS-PC for computation (9.01 v, SAS Institute, Inc, Cary, North Carolina).

**Results**

A total of 7984 live-born and stillborn infants and fetuses with CHDs meeting the MACDP case definition were included: 169 (2.1%) with cardiac looping defects, 1204 (15.1%) with conotruncal defects, 447 (5.6%) with AVSDs, 1031 (12.9%) with LVOTOs, 694 (8.7%) with RVOTOs, 1020 (12.8%) with ASDs, 3579 (44.8%) with VSDs, 157 (2.0%) with cell growth defects, and 66 (0.8%) with Ebstein anomaly. Because some infants had more than one independent CHD, the total number of individual defects was greater than the number of case infants. Among all case infants with CHDs, 5695 (71.3%) had an isolated CHD, 1080 (13.5%) had MCAs, 1048 (13.1%) had a chromosomal or single-gene determined syndrome, and 161 (2.0%) had laterality defects (Table II). In our study, 90.6% of all syndromes consisted of chromosomal anomalies. Among those with syndromes, we identified 949 case infants with chromosomal anomalies, 66 with single-gene disorders, and 10 with teratogenic syndromes. The frequency of identified noncardiac anomalies varied for different types of CHDs. We observed the highest percentage of MCAs among cases with ASDs (18.5%) and cardiac looping defects (17.2%). The highest percentage of syndromic cases was among those with AVSDs (66.7%), followed by the groups with ASDs and conotruncal defects (22.0% and 13.2%, respectively) (Table II). Our results showed that up to 87% of all cases with syndromic AVSDs were those with Down syndrome. Case infants with Ebstein anomaly had the highest proportion of isolated CHDs (90.9%), and those with AVSDs had the lowest (24.4%).

Table III shows selected demographic and clinical characteristics of case infants in each birth defects categories and during different time periods. The proportion of recognized syndromes increased from 8.0% to 14.5% over the three time periods of the study (P < .001). We observed a significantly higher proportion of syndromes and a lower proportion of case infants with isolated CHDs and case infants with MCA among mothers 35 years of age or older compared with mothers younger than 35 years of age (P < .05). Also, there was a significant difference in the proportion of types of defects among live-born infants who died after birth compared with those who did not expire after birth. Among live-born case infants with CHDs who died after birth, 50.3% had isolated CHDs, 21.8% had MCAs, 22.7% had syndromes, and 5.3% had laterality defects; among those who did not die after birth, the percentages were 74.7%, 12.2%, 11.6%, and 1.5%, respectively (P < .001). In addition, we identified a significant variation in the proportion of additional noncardiac anomalies by birth outcome. For example, among live-born case infants with CHDs, 72.4% had isolated CHDs, 13.0% has MCAs, and 12.6% had syndromes; among those stillborn, the proportions were 32.9%, 39.7%, and 25.3%, respectively, and among TOPs, 29.3%, 19.0%, and 50.0%, respectively (P < .001). We also observed a significant difference in the characteristics of case infants who had been autopsied and those who had not. Among case infants who had not been autopsied, 73.2% had isolated CHDs, 12.3% had MCAs, and 12.7% had syndromes, whereas among case infants who had been autopsied, 45.5% had isolated
The distribution of 46 individual noncardiac anomalies among cases with MCAs for all CHDs as a group and for specific CHD phenotypes is presented in Table IV. For cases with any CHDs as a group the most common noncardiac defects were of the skeletal (35.0%), gastrointestinal (25.2%), and renal or urinary systems (23.1%). We observed a similar order of frequency for AVSDs, ASDs, and VSDs. Specific MCA combinations include: any limb defects with cardiac looping, conotruncal, AVSD, LVOTO, ASDs or VSDs; esophageal or duodenal atresia/stenosis with conotruncal defects; anal or rectal atresia with LVOTO, RVOTO, ASDs or VSDs; and hydronephrosis or atresia of urethra/bladder neck with cardiac looping, RVOTO, ASDs and VSDs. There were also high frequencies of cases with AVSD and ocular or genital defects, and cases of cardiac looping or conotruncal defects and non-NTD central nervous defects (Table IV). Additionally, we examined the distribution of noncardiac anomalies among cases with MCAs that had an autopsy report. When restricting to cases with MCA that had an autopsy, among all CHDs as a group we found higher percentage of NTDs (9.1%), respiratory system defects (26.7%), renal/urinary system defects (35.8%), bilateral absence of kidneys (9.1%), all skeletal defects (46.1%), and any limb deficiency (30.9%).

**Discussion**

The objective of our study was to assess the proportion and pattern of structural noncardiac anomalies among children with CHDs from data culled from a large population-based surveillance system. Analysis of our case infants showed that 71.3% had isolated CHDs, 13.5% had an undefined pattern of MCAs, 13.1% had specific syndromes, and 2.0% had laterality defects. The proportion with MCAs was well within the range reported by other epidemiologic studies (5.9% to 14.1%).1,10,12 The slight difference in percentages between these reports and our study might have been attributable to the different case definitions, inclusion criteria, and class classifications used across the studies. However, direct comparison between studies was difficult due to methodological differences. Some of the older studies failed to distinguish specific types of noncardiac anomalies at all, and syndromes, sequences, and malformations often were grouped together.
The frequency of additional noncardiac anomalies varied for different types of CHDs, with the highest proportion of MCAs observed among those with ASDs, cardiac looping defects, and conotruncal defects. Previous reports of population-based epidemiological studies have shown a high proportion of multiple defects (approximately 18% to 52%) among patients with ASDs.2,20 However, no biological explanation for this finding has been proposed. This wide range of proportions certainly has been due to different inclusion criteria for malformations and the proportions calculated. For example, Bosi et al20 presented the percentage of multiple defects (approximately 18%) among all case participants with CHDs, and Pradat2 calculated the percentage of multiple defects (52%) excluding syndromes. Earlier studies also have reported high percentages of MCAs among specific phenotypes within the cardiac looping (eg, single ventricle, 37.4%)2 and conotruncal categories (eg, truncus arteriosus, 9.1% to 45.6%; interrupted aortic arch, 41.3%; double-outlet right ventricle, 20.0% to 33.9%; and tetralogy of Fallot, 13.5% to 32.2%).1,2 A plausible explanation for those findings is that such defects occur at the earliest stages of morphogenesis and therefore disturb the primary developmental field, which could result in multiple and complex defects of morphogenesis.21 In our study, cases with Ebstein anomaly, cell growth defects, RVOTOs, LVOTOs, and VSDs showed the lowest percentages of MCAs and syndromes and the highest percentages of isolated defects, similar to findings from the Baltimore-Washington Infant Study,1 suggesting potentially later developmental timing during gestation. For instance, Ebstein anomaly might be caused by abnormalities of programmed cell death, which occur in the later stages of cardiogenesis.16 In this study, the low proportion of MCAs among cases with VSDs (12.8%), similar to what has been reported by other published studies (6.5% to 9.5%),1,12,22 probably reflected the fact that most VSDs are of the muscular type and usually found in isolation.

**Table III. Demographic and clinical characteristics of congenital heart defects by presence and type of associated noncardiac anomalies, Metropolitan Atlanta Congenital Defects Program, 1968 to 2005**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Isolated defects</th>
<th>MCAs*</th>
<th>Syndromes†</th>
<th>Laterality defects</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1968–1980</td>
<td>959 (72.7)</td>
<td>222 (16.8)</td>
<td>105 (8.0)</td>
<td>33 (2.5)</td>
<td>1319 (16.5)</td>
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<tr>
<td>1981–1992</td>
<td>1492 (70.3)</td>
<td>300 (14.1)</td>
<td>284 (13.4)</td>
<td>47 (2.2)</td>
<td>2123 (26.6)</td>
</tr>
<tr>
<td>1993–2005</td>
<td>3244 (71.4)</td>
<td>558 (12.3)</td>
<td>659 (14.5)</td>
<td>81 (1.8)</td>
<td>4542 (56.9)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>3019 (73.1)</td>
<td>566 (13.7)</td>
<td>483 (11.7)</td>
<td>63 (1.5)</td>
<td>4131 (52.1)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1952 (68.5)</td>
<td>403 (14.1)</td>
<td>417 (14.6)</td>
<td>79 (2.8)</td>
<td>2851 (36.0)</td>
</tr>
<tr>
<td>Other</td>
<td>681 (71.9)</td>
<td>108 (11.4)</td>
<td>140 (14.8)</td>
<td>18 (1.9)</td>
<td>947 (11.9)</td>
</tr>
<tr>
<td>Maternal age &lt;35 years</td>
<td>4865 (72.8)</td>
<td>930 (13.9)</td>
<td>748 (11.2)</td>
<td>142 (2.1)</td>
<td>6665 (84.1)</td>
</tr>
<tr>
<td>Maternal age ≥35 years</td>
<td>806 (63.7)</td>
<td>145 (11.5)</td>
<td>296 (23.4)</td>
<td>18 (1.4)</td>
<td>1265 (15.9)</td>
</tr>
<tr>
<td>Infant sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2851 (71.8)</td>
<td>572 (14.4)</td>
<td>479 (12.1)</td>
<td>70 (1.8)</td>
<td>3972 (49.8)</td>
</tr>
<tr>
<td>Female</td>
<td>2842 (71.1)</td>
<td>501 (12.5)</td>
<td>566 (14.2)</td>
<td>91 (2.3)</td>
<td>4000 (50.2)</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Singleton</td>
<td>5374 (71.2)</td>
<td>1005 (13.3)</td>
<td>1014 (13.4)</td>
<td>158 (2.1)</td>
<td>7551 (94.7)</td>
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<tr>
<td>Twins or higher</td>
<td>316 (74.2)</td>
<td>73 (17.1)</td>
<td>34 (8.9)</td>
<td>3 (0.7)</td>
<td>450 (63.5)</td>
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<tr>
<td>Died after birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>554 (50.3)</td>
<td>240 (21.8)</td>
<td>250 (22.7)</td>
<td>58 (5.3)</td>
<td>1102 (13.8)</td>
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<tr>
<td>No</td>
<td>5141 (74.7)</td>
<td>840 (12.2)</td>
<td>798 (11.6)</td>
<td>103 (1.5)</td>
<td>6882 (86.2)</td>
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<td>Birth outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>5629 (72.4)</td>
<td>1010 (13.0)</td>
<td>982 (12.6)</td>
<td>157 (2.0)</td>
<td>7777 (97.4)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>469 (32.9)</td>
<td>58 (39.7)</td>
<td>37 (25.3)</td>
<td>3 (2.1)</td>
<td>146 (19.8)</td>
</tr>
<tr>
<td>TOP*</td>
<td>17 (23.3)</td>
<td>11 (19.0)</td>
<td>29 (50.0)</td>
<td>1 (1.7)</td>
<td>56 (7.7)</td>
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<tr>
<td>Autopsy</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>248 (45.5)</td>
<td>165 (30.3)</td>
<td>105 (19.3)</td>
<td>27 (5.0)</td>
<td>545 (6.8)</td>
</tr>
<tr>
<td>No</td>
<td>5447 (73.2)</td>
<td>915 (12.3)</td>
<td>943 (12.7)</td>
<td>134 (1.8)</td>
<td>7439 (93.2)</td>
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<td>Gestational age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Preterm</td>
<td>1189 (61.3)</td>
<td>389 (20.0)</td>
<td>323 (16.6)</td>
<td>40 (2.1)</td>
<td>1941 (24.7)</td>
</tr>
<tr>
<td>Term</td>
<td>4420 (74.8)</td>
<td>667 (11.3)</td>
<td>706 (11.9)</td>
<td>118 (2.0)</td>
<td>5911 (75.3)</td>
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<tr>
<td>Birth weight ≥2500</td>
<td>1169 (56.5)</td>
<td>432 (20.9)</td>
<td>431 (20.8)</td>
<td>37 (1.8)</td>
<td>2069 (26.1)</td>
</tr>
<tr>
<td>≤2500</td>
<td>4508 (76.9)</td>
<td>636 (10.8)</td>
<td>594 (10.1)</td>
<td>124 (2.1)</td>
<td>5862 (73.9)</td>
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<tr>
<td>Prior pregnancy loss</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No prior loss</td>
<td>3390 (70.9)</td>
<td>610 (12.8)</td>
<td>683 (14.3)</td>
<td>96 (2.0)</td>
<td>4779 (86.4)</td>
</tr>
<tr>
<td>At least one prior loss</td>
<td>536 (71.4)</td>
<td>102 (13.6)</td>
<td>99 (13.2)</td>
<td>14 (1.9)</td>
<td>751 (13.6)</td>
</tr>
</tbody>
</table>

*Multiple congenital anomalies.
†Chromosomal syndromes, single-gene disorders, and recognized conditions.
zRow percent.
xColumn percent.
TOP Termination of pregnancy.

The frequency of additional noncardiac anomalies varied for different types of CHDs, with the highest proportion of MCAs observed among those with ASDs, cardiac looping defects, and conotruncal defects. Previous reports of population-based epidemiological studies have shown a high proportion of multiple defects (approximately 18% to 52%) among patients with ASDs.2,20 However, no biological explanation for this finding has been proposed. This wide range of proportions certainly has been due to different inclusion criteria for malformations and the proportions calculated. For example, Bosi et al20 presented the percentage of multiple defects (approximately 18%) among all case participants with CHDs, and Pradat2 calculated the percentage of multiple defects (52%) excluding syndromes. Earlier studies also have reported high percentages of MCAs among specific phenotypes within the cardiac looping (eg, single ventricle, 37.4%)2 and conotruncal categories (eg, truncus arteriosus, 9.1% to 45.6%; interrupted aortic arch, 41.3%; double-outlet right ventricle, 20.0% to 33.9%; and tetralogy of Fallot, 13.5% to 32.2%).1,2 A plausible explanation for those findings is that such defects occur at the earliest stages of morphogenesis and therefore disturb the primary developmental field, which could result in multiple and complex defects of morphogenesis.21 In our study, cases with Ebstein anomaly, cell growth defects, RVOTOs, LVOTOs, and VSDs showed the lowest percentages of MCAs and syndromes and the highest percentages of isolated defects, similar to findings from the Baltimore-Washington Infant Study,1 suggesting potentially later developmental timing during gestation. For instance, Ebstein anomaly might be caused by abnormalities of programmed cell death, which occur in the later stages of cardiogenesis.16 In this study, the low proportion of MCAs among cases with VSDs (12.8%), similar to what has been reported by other published studies (6.5% to 9.5%),1,12,22 probably reflected the fact that most VSDs are of the muscular type and usually found in isolation.
<table>
<thead>
<tr>
<th>Associated anomaly</th>
<th>All CHDs*</th>
<th>Cardiac looping defects</th>
<th>Conotruncal defects</th>
<th>TOF†</th>
<th>AVSVDs§</th>
<th>LVOTs**</th>
<th>Coarctation of aorta</th>
<th>HLHS†</th>
<th>RVOTs††</th>
<th>Pulmonary Valve stenosis</th>
<th>ASDs**</th>
<th>ASDs secundum</th>
<th>VSDs††</th>
<th>VSDs muscular</th>
<th>VSDs pericardial defect</th>
<th>Membranous</th>
<th>Cell growth</th>
<th>Ebstein anomaly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated anomaly</td>
<td>All CHDs*</td>
<td>Cardiac Looping defects</td>
<td>Conotruncal Defects</td>
<td>TOF†</td>
<td>AVSDs‡</td>
<td>LVOTOs§</td>
<td>Coarctation of aorta</td>
<td>HLHS‡</td>
<td>RVOTOs†</td>
<td>Pulmonary Valve Stenosis</td>
<td>ASDs**</td>
<td>ASDs secundum</td>
<td>VSDs††</td>
<td>VSDs muscular</td>
<td>VSDs peri membranous</td>
<td>Cell growth</td>
<td>Ebstein anomaly</td>
<td></td>
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<td>--------------------------------------------------------</td>
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<td></td>
</tr>
<tr>
<td>Any limb deficiency</td>
<td>201 (18.6)</td>
<td>7 (24.1)</td>
<td>37 (19.2)</td>
<td>18</td>
<td>12</td>
<td>30</td>
<td>19 (11.6)</td>
<td>9</td>
<td>14</td>
<td>7</td>
<td>14</td>
<td>20</td>
<td>9</td>
<td>32</td>
<td>40</td>
<td>100</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Longitudinal limb deficiency</td>
<td>29 (2.7)</td>
<td>1 (3.4)</td>
<td>8</td>
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<td>2</td>
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<td>3</td>
<td>100</td>
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<tr>
<td>Other and unspecified limb deficiencies</td>
<td>97 (9.0)</td>
<td>3 (3.0)</td>
<td>19 (8.8)</td>
<td>12</td>
<td>6</td>
<td>13 (8.3)</td>
<td>7 (8.3)</td>
<td>5</td>
<td>2</td>
<td>3 (4.6)</td>
<td>22</td>
<td>11</td>
<td>9</td>
<td>4</td>
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<td>Upper limb deficiency</td>
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<td>8</td>
<td>4</td>
<td>3</td>
<td>5</td>
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<td>2 (3.4)</td>
<td>2</td>
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<td>1</td>
<td>5</td>
<td>9</td>
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<tr>
<td>Lower limb deficiency</td>
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<td>2 (2.4)</td>
<td>2</td>
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<td>1 (1.5)</td>
<td>9 (4.8)</td>
<td>5</td>
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<td>17</td>
<td>4</td>
<td>300</td>
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<td>Congenital dislocation/dysplasia of hip</td>
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<td>1</td>
<td>0.5</td>
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<td>2 (2.5)</td>
<td>4 (2.8)</td>
<td>3</td>
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<td>1 (2.0)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>200</td>
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<tr>
<td>Club foot (excl NTDs)</td>
<td>74 (6.9)</td>
<td>12 (6.2)</td>
<td>5</td>
<td>4.9</td>
<td>1</td>
<td>2 (2.5)</td>
<td>7 (4.5)</td>
<td>4</td>
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<td>2 (4.1)</td>
<td>5 (5.1)</td>
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<td>4 (4.6)</td>
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<td>9 (7.9)</td>
<td>39</td>
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<td>Any hand defects</td>
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<td>3 (10.3)</td>
<td>12</td>
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<td>4</td>
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<td>5</td>
<td>7 (7.7)</td>
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<td>9</td>
<td>4.7</td>
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<td>6 (6.4)</td>
<td>6</td>
<td>8</td>
<td>3 (3.0)</td>
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<td>2</td>
<td>3 (3.1)</td>
<td>7 (7.9)</td>
<td>2 (1.8)</td>
<td>18</td>
<td>(3.9)</td>
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<td>Syndactyly</td>
<td>45 (4.2)</td>
<td>8 (4.1)</td>
<td>3</td>
<td>2.9</td>
<td>2</td>
<td>5 (0.5)</td>
<td>8 (5.1)</td>
<td>6</td>
<td>7</td>
<td>2 (4.1)</td>
<td>6 (6.1)</td>
<td>5</td>
<td>7 (7.7)</td>
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<td>21 (4.6) 1</td>
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<td>Muscular/asbestos</td>
<td>77 (7.1)</td>
<td>5 (17.2)</td>
<td>15</td>
<td>7.8</td>
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<td>9.9</td>
<td>1 (2.5)</td>
<td>13</td>
<td>8</td>
<td>3 (3.0)</td>
<td>1 (1.5)</td>
<td>13</td>
<td>8 (7.0)</td>
<td>31 (6.8)</td>
<td>8 (5.5)</td>
<td>10 (8.7) 2</td>
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<td>Diaphragmatic hernia</td>
<td>37 (3.4)</td>
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<td>10 (6.4)</td>
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<td>6 (3.2)</td>
<td>3 (2.6)</td>
<td>15 (3.3) 4</td>
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<td>Omphalocele</td>
<td>38 (3.5)</td>
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<td>10</td>
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<td>2 (6.1)</td>
<td>4 (4.5)</td>
<td>16 (3.5)</td>
<td>2 (1.4) 5</td>
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<td>1.0</td>
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<td>1 (0.5)</td>
<td>1 (1.0)</td>
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<td>1</td>
<td>1 (1.5)</td>
<td>2 (1.1)</td>
<td>1</td>
<td>1 (0.9)</td>
<td>2 (0.4)</td>
<td>2 (1.4)</td>
<td>1 (0.5) 1</td>
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<tr>
<td>Cystic hygroma</td>
<td>13 (1.2)</td>
<td>2 (6.9)</td>
<td>4</td>
<td>2.5</td>
<td>1</td>
<td>1 (2.0)</td>
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<td>1</td>
<td>2</td>
<td>2 (4.1)</td>
<td>1 (1.5)</td>
<td>18</td>
<td>9 (5.5)</td>
<td>9 (7.9)</td>
<td>28 (6.1)</td>
<td>10 (6.8) 8</td>
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<tr>
<td>VACTERL</td>
<td>62 (5.7)</td>
<td>2 (6.9)</td>
<td>16</td>
<td>8.3</td>
<td>6</td>
<td>5.9</td>
<td>6 (3.8)</td>
<td>5</td>
<td>6</td>
<td>3 (3.0)</td>
<td>1 (1.5)</td>
<td>18</td>
<td>9 (5.5)</td>
<td>28 (6.1)</td>
<td>10 (6.8)</td>
<td>8 (7.0) 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total defects</td>
<td>1080</td>
<td>29 (100)</td>
<td>193 (100)</td>
<td>102 (100)</td>
<td>100 (100)</td>
<td>157 (100)</td>
<td>84 (100)</td>
<td>49 (100)</td>
<td>99 (100)</td>
<td>65 (100)</td>
<td>189 (100)</td>
<td>114 (100)</td>
<td>458 (100)</td>
<td>146 (100)</td>
<td>115 (100)</td>
<td>20 (100)</td>
<td>4 (100)</td>
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*Congenital heart defects. †Tetralogy of Fallot. ‡Atrioventricular septal defects. §Left ventricular outflow tract obstructions. ¶Hypoplastic left heart syndrome. ¶¶Right ventricular outflow tract obstructions. **Atrial septal defects. ††Ventricular septal defects. Column percent. If an infant had more than one defect in the same organ system group, the infant would be counted once for the overall organ system group. Overall organ system groups and individual defects were not mutually exclusive. Infants with defects of more than one organ system were counted separately under each organ system.
among otherwise healthy children. Additionally, the observation of a very high proportion of cases with syndromes among those with AVSDs corroborates previous observations of the well-known association of AVSDs with Down syndrome.12,18,20,22

Our results reflected the general tendency of more frequent and improved chromosomal analysis and molecular testing in recent decades, including that for 22q11 deletion.4,19 In our study, 16% of case infants with DiGeorge syndrome did not have cytogenetic results through 1990. Since 1968, the proportion of mothers older than 30 years of age among this population has more than doubled, from 16% to 42% in 2005.7 Our finding of a higher proportion of syndromes among children of mothers 35 years of age or older was in agreement with the well-known association of chromosomal anomalies due to nondisjunction and advanced maternal age.23

Similar to findings of previous studies,1,5,7,9,10 our analysis showed higher percentages of multiple noncardiac defects among case infants who were autopsied. This most probably reflected the more thorough investigation of infants who underwent autopsies and the severity of additional noncardiac defects among live-born infants who died, stillbirths, and elective TOPs because of a prenatal diagnosis of defects. A study by Tennstedt et al,5 based on necropsy results, reported the highest proportion of MCAs among fetuses from induced abortions, spontaneous abortions, and stillbirths. According to Bull et al,24 case infants with severe CHDs, such as hypoplastic left heart syndrome, AVSDs, and single-ventricle defects, were recognized most frequently antenatally; the overall TOP rate among these case infants was 50%. Thus, TOP might be a proxy for severity of CHDs as well as a proxy for MCAs. As previously reported,25,26 we found that additional noncardiac anomalies occurred more frequently among premature infants and newborn infants with low birth weight.

Our results showed that the most frequent noncardiac anomalies among MCA case infants were any skeletal defects (35.0%), followed closely by gastrointestinal (25.2%) and renal defects (23.1%). Although these results were in agreement with those of some previous studies showing the musculoskeletal (8.8% to 25.3%)12,22,27,28 and gastrointestinal (12.7% to 25.3%)29,30 as the most commonly affected organ systems, they differed with the results of another study that showed craniofacial defects (19.7%) as the most prevalent of defects.7 The frequent association of CHDs and skeletal defects might reflect a common pathogenetic mechanism involving early differentiation and migration of mesodermal cells.31,32 Similarly, simultaneous occurrence of conotruncal defects and gastrointestinal system anomalies might reflect disturbances of neural crest cell migration.4,33 It also is possible that the differences in the frequencies of the types of MCAs noted among different studies reflected differences in case ascertainment and classification. Nonetheless, the precise pathogenesis for the observed patterns remains largely unknown.

Ours was a systematic, population-based study assessing the association between distinct phenotypic categories of CHDs and different groups of noncardiac defects among case infants with no previously defined patterns of MCAs. In addition, our study included cases with CHDs among live-born and stillborn infants and TOPs from a defined population ascertained by a surveillance system with active case finding and high sensitivity34; thus, it represented a more inclusive group of cases than usually has been reported by studies based on clinic populations or other surveillance programs. Furthermore, a clinical, standardized nomenclature and developmental schema was used to classify heart defects and eliminate nonstructural and newborn or prematurity-associated cardiac conditions,15 and cases with additional noncardiac anomalies were reviewed by a clinical geneticist.

Our study had several limitations as well. First, advanced cytogenetic techniques and molecular studies were not available during the earlier periods reviewed as part of our study. Therefore, small structural cytogenetic abnormalities and single-gene mutations might have remained undiagnosed, resulting in the inadvertent inclusion of some genetically determined case infants among the MCA group. Diagnostic differences over time have affected birth defect ascertainment by MACDP. Also, because MACDP does not routinely gather information on risk factors, the number of teratogenic syndromes (eg, fetal alcohol syndrome) might have been underestimated. Second, although we stratified maternal race as white, black or African American, or other, we did not have detailed information on Hispanic ethnicity until 1973; thus, our categories of race and ethnicity were not homogeneous across all the study years.14 Our defect classification was based on the clinical information contained in medical records. To minimize the possibility of potential misclassification resulting from the use of International Classification of Diseases, Ninth Revision codes for broad groups, we used an expanded coding system and standardized nomenclature. Last, severe birth defects often are identified prenatally, but fetuses of pregnancies that are terminated after diagnosis of a defect often do not have autopsy evaluations or as comprehensive an evaluation as live-born infants who die. The autopsy evaluation had a great effect on the number and pattern of reported defects and was not performed systematically among MACDP case infants. In addition, the sample size for some of the CHD phenotypes and specific malformations was relatively small. Thus, specific CHD phenotypes and individual noncardiac defects had to be lumped into broad categories for analysis, which might have limited the interpretation of some of the results. We did not examine the patterns of multiple noncardiac defects for the same infant. Also, because multiple statistical tests were performed, some of the observed statistically significant associations might have been due to chance.

Among case infants with CHDs, 28.7% had another major noncardiac malformation, including syndromes and laterality defects. Thus, infants with CHDs warrant careful
examination for the presence of noncardiac anomalies to facilitate early detection and management of associated major anomalies.

We thank the Metropolitan Atlanta Congenital Defects Program abstractors for their conscientious and skilled data collection efforts.

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11. Allen HD, Driscoll D, Shaddy RE, Feltes TF, Moss and Adam’s Heart Disease in the Young. Philadelphia: Lippincot Williams & Wilkins; 2008.


<table>
<thead>
<tr>
<th>Broad group</th>
<th>Individual defect</th>
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</table>
| **Cardiac Looping**               |Congenitally corrected TGA (l-TGA)  
I-TGA with VSD  
I-TGA with VSD-LVOTO  
AV discordance, without I-TGA  
Single ventricle, DILV, NOS  
Single ventricle, DILV, I-malposition  
Single ventricle, DILV, d-malposition  
Single ventricle, DIRV  
Single ventricle, mitral atresia with aortic malposition  
Single ventricle, tricuspid atresia with aortic malposition  
Single ventricle, other  
Single ventricle, NOS |
| **Conotruncal**                   |AP window (aortopulmonary window)  
DORV, VSD type  
DORV, remote VSD (uncommitted VSD)  
DORV, NOS  
d-TGA, IVS  
d-TGA, IVS-LVOTO  
d-TGA, VSD  
d-TGA, VSD-LVOTO  
d-TGA, NOS  
DORV, TGA type  
TOF  
TOF, absent pulmonary valve  
Pulmonary atresia, VSD (including TOF, PA)  
Pulmonary atresia, VSD-MAPCA (pseudotruncus)  
DORV, TOF type  
Pulmonary artery origin from ascending aorta (hemitruncus)  
Interrupted aortic arch, Type B  
Interrupted aortic arch, NOS  
Truncus arteriosus  
Vascular ring (double arch)  
Right arch, aberrant left subclavian  
Pulmonary artery sling  
VSD, Type I (subarterial, supracristal, conal septal, infundibular)  
VSD, Type III (inlet)  
AVC (AVSD), complete CAVSD  
AVC (AVSD), intermediate (transitional)  
AVC (AVSD), partial (incomplete) (PASVSD) (ASD, primum)  
AVC (AVSD), NOS  
TOF, AVC (AVSD)  
Single ventricle, unbalanced AV canal, right  
Single ventricle, unbalanced AV canal, left |
| **Atrioventricular septal defects**|Aortic stenosis, valvar  
Aortic stenosis, NOS  
Aortic valve atresia  
Aortic valve, other (dysplastic valve)  
*Isolated bicuspid aortic valve  
Coarctation of aorta  
Aortic arch hypoplasia  
Interrupted aortic arch, Type A  
Hypoplastic left heart syndrome (HLHS)  
*Supravalvular main PA stenosis (trunk)  
*Pulmonary artery stenosis, branch, central  
*Pulmonary artery stenosis, branch, peripheral (beyond the hilar bifurcation)  
*Pulmonary artery stenosis, NOS  
Pulmonary stenosis, valvar  
Pulmonary stenosis, NOS  
Pulmonary valve, other (dysplastic valve)  
Pulmonary atresia, IVS  
Single ventricle, tricuspid atresia  
Double-chambered RV  
ASD, NOS  
ASD, secundum  
VSD, Type IV (muscular)  
VSD, NOS  
VSD, Type II (perimembranous)  
ASD, sinus venosus  
Cor tristriatum  
Partial anomalous pulmonary venous connection (PAPVC) |
| **Left ventricular outflow tract obstruction**|Aortic stenosis, valvar  
Aortic stenosis, NOS  
Aortic valve atresia  
Aortic valve, other (dysplastic valve)  
*Isolated bicuspid aortic valve  
Coarctation of aorta  
Aortic arch hypoplasia  
Interrupted aortic arch, Type A  
Hypoplastic left heart syndrome (HLHS)  
*Supravalvular main PA stenosis (trunk)  
*Pulmonary artery stenosis, branch, central  
*Pulmonary artery stenosis, branch, peripheral (beyond the hilar bifurcation)  
*Pulmonary artery stenosis, NOS  
Pulmonary stenosis, valvar  
Pulmonary stenosis, NOS  
Pulmonary valve, other (dysplastic valve)  
Pulmonary atresia, IVS  
Single ventricle, tricuspid atresia  
Double-chambered RV  
ASD, NOS  
ASD, secundum  
VSD, Type IV (muscular)  
VSD, NOS  
VSD, Type II (perimembranous)  
ASD, sinus venosus  
Cor tristriatum  
Partial anomalous pulmonary venous connection (PAPVC) |
| **Right ventricular outflow tract obstruction**|Aortic stenosis, valvar  
Aortic stenosis, NOS  
Aortic valve atresia  
Aortic valve, other (dysplastic valve)  
*Isolated bicuspid aortic valve  
Coarctation of aorta  
Aortic arch hypoplasia  
Interrupted aortic arch, Type A  
Hypoplastic left heart syndrome (HLHS)  
*Supravalvular main PA stenosis (trunk)  
*Pulmonary artery stenosis, branch, central  
*Pulmonary artery stenosis, branch, peripheral (beyond the hilar bifurcation)  
*Pulmonary artery stenosis, NOS  
Pulmonary stenosis, valvar  
Pulmonary stenosis, NOS  
Pulmonary valve, other (dysplastic valve)  
Pulmonary atresia, IVS  
Single ventricle, tricuspid atresia  
Double-chambered RV  
ASD, NOS  
ASD, secundum  
VSD, Type IV (muscular)  
VSD, NOS  
VSD, Type II (perimembranous)  
ASD, sinus venosus  
Cor tristriatum  
Partial anomalous pulmonary venous connection (PAPVC) |
| **Atrial septal defects**          |ASD, NOS  
ASD, secundum|
| **Ventricular septal defects**     |VSD, Type IV (muscular)  
VSD, NOS  
VSD, Type II (perimembranous)  
ASD, sinus venosus  
Cor tristriatum  
Partial anomalous pulmonary venous connection (PAPVC) |
| **Cell growth**                    |ASD, NOS  
ASD, secundum  
VSD, Type IV (muscular)  
VSD, NOS  
VSD, Type II (perimembranous)  
ASD, sinus venosus  
Cor tristriatum  
Partial anomalous pulmonary venous connection (PAPVC) |
### Appendix. Continued

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<th>Individual defect</th>
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<td>Partial anomalous pulmonary venous connection (PAPVC), scimitar</td>
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